Book 1

Dear Mr. President:

COVID-19 and Where We Went Wrong

Charles H. Andrus, M.D., F.A.C.S. February 2, 2023

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BOOK 1, Volume 1, 0.5-28 Chapters

Dear Mr. President: COVID-19 and Where We Went Wrong

Charles H. Andrus, M.D., F.A.C.S. February 2, 2023

Book 1 of 3 books that were initially transmitted 9/24/2022: Dear Mr. President: COVID-19 and Where We Went Wrong

Other Books:

Book 2 of 3 books that were initially transmitted 9/24/2022:

Combined pdf submission of 9/24/2022

Book 3 of 3 books that were initially transmitted 9/24/2022:

Dear Mr. President ... To Care for Him Who Shall Have Borne the Battle A. Lincoln

For educational purposes of the People of the United States of America

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150 Emerald Green Ct St. Louis, MO. 63141 September 24, 2022

> Home: (314) 455-9482 Pam's cell: 314-809-9634

President Joseph Biden
President of the United States of America
The White House
1600 Pennsy Ivania Avenue
Washington, D.C. 20500
202-456-1414

Re: NIHNIAID Case #12276

USPS Priority mail

2022-09-24 Abandoning Patients and Violating the intent of Primum non Nocere

Dear Mr. President

Over the last two and half years, all Physicians of American by withholding an organized, <u>early</u> (within <72 hours of diagnosis) standard of TREATMENT with immunoglobulins (Passive Immunization) and antivirals have disregarded their oaths of *Primum non Nocere*. We have abandoned the individual patient collectively by obfuscation and *de facto* rationing of the antivirals and by discounting past Medical History with regards to Passive Immunization (COVID-19 Convalescent Plasma - exogenous polyclonal antibodies). Organized, uniform **EARLY TREATMENT** with immunoglobulins and/or antivirals of every man, woman, and child early in the course of their COVID-19 infection (within <72 hours of diagnosis) has been relegated to the historical scrapheap facilitated by waivers of EMTALA retroactive to 3/1/2020; individual and corporation greed and financial advancement; protecting the research *status quo* of the *placebo* by the FDA, NIH, DARPA, USPHS, DOD, VA, etc. in funded Clinical Research Trials, the FDA and NIH ignored The Right to Try Act of 2018, PL-115-176; and ignorance, heartlessness, and just plain meanness.

Mr. President, we should be thanking God that:

- (1) in 1885, Louis Pasteur treated Joseph Meister with rabies convalescent plasma (polyclonal convalescent plasma);
- (2) in the 1970s, the WHO eradicated small pox from the World by Passive Immunization (small pox convalescent plasma) in those newly infected and with Active Immunization (vaccination) in the uninfected; and
- (3) in 1968, the researchers of Columbia University, New York City, New York, developed and initiated the treatment with Rhogam (pooled sera from Rh negative sensitized mothers) of postpartum Rh negative mothers within 72 hours of delivery so

that in the United States today: *hydrops fetalis* has become a present-day, medical historical rarity.

Mr. President over a million people are dead and millions more maimed for life due to the morbidities of COVID-19 since the meeting in *The White House* on March 2, 2020, where there was **NO** mention of COVID-19 Convalescent Plasma (CCP), **NO** representatives of the >5000 Blood Banks of America (e.g.: the American Red Cross, etc.) were present, and **NO** suggestion of a Federally-organized National Plasma Drive to collect CCP proclaimed by the President of the United States. https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus; Transcript of the meeting of 3/2/2020:

https://web.archive.org/web/20200303160403/https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/

Attached to this cover letter is a table containing the accumulating cases and deaths over time versus the major accomplishments, misdirections, and failures in our COIVD-19 fight of the United States of America. As I am a federal physician and surgeon, it is my duty to provide this *educational information* to the people of the United States of America. Any personal copyright privileges I may have to this material, I waive to the people of the United States of America, the government of the United States, and to you, Mr. President. Mr. President we need to recognize where we have faltered and move to "right-correct"-our-country coherent with the intent of President Lincoln admonition of March 4, 1865:

With malice toward none, with charity for all, with firmness in the right as God gives us to see the right, let us strive on to finish the work we are in, to bind up the nation's wounds, to care for him who shall have borne the battle and for his widow and his orphan, to do all which may achieve and cherish a just and lasting peace among ourselves and with all nations.

Mr. President, thank you for considering all the submission that follows this cover letter.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.

harler H. Andres MD

Physician and Surgeon

Veterans Health Administration

U.S. Department of Veterans Affairs

/Volumes/NIAID12276/2022-09-22 9-23Final submission to NIAID file 12276/1.0 Dear Mr. President COVID-19 and where we went wrong age 000 of 2000-09-23 calculations owid-covid-data (5).xlsx

Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total_U.S. Cases since 1/22/2020	Total_U.SD eaths since 1/22/2020
2020-02-24	Wu Z, McGoogan JM: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) Outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. Doi:10:1001/jama.2020.2648. https://jamanetwork.com/journals/jama/fullarticle/2762130 (THIS IS THE ARTICLE IN WHICH OFFICIALLY THE U.S. FDA INCORRECTLY BASED THE ELIGIBILITY CRITERIA FOR THE ADMINISTRATION OF COVID-19 CONVALESCENT PLASMA that remained official from March 24, 2020 to September 2, 2020.	16	*
2020-03-01	Retroactive EMTALA waivers (Ref 344, 347)	32	1
2020-03-02	WH meeting which did not include the AMERICAN RED CROSS. Dr. Schleifer confuses "passive vaccination" with "passive immunity" failing to mention Convalescent Plasma as an EARLY TREATMENT (<72 hours) (Ref: 332, 333, 334, 335, 336 two minutes of WH meeting (https://www.youtube.com/watch?v=31i6p_stzW8), (Ref337)	55	6
2020-03-13	President Trump declares Public Health Emergency (PHE). (Ref 347, 350)	2219	51
2020-03-14	China sends experts to Italy (Ref 345)	2978	58
2020-03-19	Surgeon General Adams Public Service Announcement (PSA). (Ref 352) & Johns Hopkins documents China sends 90 tons CCP to Italy (Ref 353)	13663	266
2020-03-24	FDA (WRONG) Inclusion Criteria based on wrong interpretation and thus wrong application (Ref 362, 373)	56714	. 1033
2020-03-25		68841	1366
2020-03-26		86662	1783
2020-03-27		105253	2305
2020-04-01	Norah O'Donnell of CBS News states to Dr Fauci: With all due respect it does seem like so much of this we're making it up as we go along. (Ref 385, 413)	227898	6996
2020-04-04	FDA/Mayo Clinic Expanded Access Protocol for COVID-19 (Ref 393)	324341	11593
2020-04-08	FDA announces FDA/Mayo Clinic Expanded Access with Inclusion criteria based on WRONG TIME of administration. (Ref 403, 404)	446505	19737
2020-04-16	Wired, News Archives UK: The blood of coronavirus survivors could help cope with the pandemic. https://www.wired.co.uk/article/coronavirus-blood-plasmatrials (Ref 413)	683357	37487
2020-04-24	President Trump overshadows CCP talking about possible IV disinfectants (Ref: 425)	918954	55195
2020-05-01	President Trump announces Remdesivir. (Ref 431-434, 437, 441, 445,448)	1115889	68513
2020-05-14	Joyner et al safety report of the first 5000 patients in FDA/ Mayo Clinic Expanded Access (compassionate use) protocol (Ref 464)	1424855	89558
2020-06-02	European Blood Alliance: COVID-19 Convalescent Plasma (Ref 480, 481)	1828871	109582
2020-06-08	Dr. Fauci speaks with JAMA (Ref 486) and Dr. Andrus submits: Time: The Crucial Independent Variable of the COCVID-19 Pandemic, US Copyright Office Txu002199029. (Ref 487)	1956980	114050
2020-06-09	Kara Harris responding for Dr. Fauci establishes NIH NIAID Case #12276. (Ref 490)	1977325	114959
6/19/20	K. McEnany in WH press conference reiterating that "Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promisingthis has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages" (Ref 495)	2222188	121748
	DHHS Secretary Azar pleads on CNN for COVID-19 Convalescent Plasma and then pushes to dismantling of the ACA. (Ref 503)	2557309	126496

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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total_U.S. Cases since 1/22/2020	Total_ U.S D eaths since 1/22/2020
2020-07-07	Casadevall, Joyner, Pirofski: SARS-Co V-2 viral load and antibody responses: the case for convalescent plasma therapy. (Ref 508). And Regeneron receives an additional \$450 million lo produce monoclonal antibody cocktail (Regeneron had received al least \$400 million for R&Dearlier in 2020) Ref 316,317,336 348,351,374,478,491,509, 510, 51 I, 549	3006192	131698
2020-07-19	Joyner et al safety report of the first 20,000 patients in FDN Mayo Clinic Expanded Access (compassionate use) protocol (Ref 521)	3768319	141176
2020-07-22	Dr. Andrus submits: <i>The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma</i> US Copyright Office Txu0022 I4049. (Ref 522)	3965007	144026
2020-07-30	President Trump visits the American Red Cross to highlight need for convalescent plasma during COVID-I9. (Ref 527,528,529,530), 531,532,534,535,536,538,539,541,542)	4485123	152751
2020-08-12	Two Washington U. doctors lead national effort to study new COVID-19 treatment, in which Highly Unethical statement made regards to research coercion: "If you have a 50% chance of gelling either the stuffor nothing, which would you choose?" (Ref 543) and Joyner ct al 3-month update on Mayo Clinic/ FDA Expanded Access (comoassionate use) Protocol (Ref 544)	52138 I I	165984
2020-08-23	Presiden Trump News Conference day before RNC to promote COVID-19 Convalescent Plasma (CCP) essentially <u>POTS AN END TO</u> THE FDA/ MA YO CLINIC EXPANDED ACCESS PROTOCOL. (Ref 551) Research and Academic Medicine disapproves and Trump team does damage control [and FDA proceeds] (Ref 552,553,554,555,556,557,558,560,561,562,563)	5721417	176027
2020-08-24	Dr Andrus on 8-23-2020 submits letter to U.S. Senate: Thousands of Americans are needless dying because the FDA is illegally ignoring PL 115-176-The Right Io Try Law! ,2 and COVID-19 Convalescent Plasma has NOT been given as Prophylaxis and Early after COVID-19 positivity conversion. Letter mailed to President Trump and the offices of the U.S. Senate. [In the attached CD: 06 Appendices A-H cony/0 I Dear Members of Congress and President Trump 8 23 20201	5755517	176460
2020-08-28	Letter to the Ofliccs of the U.S. House of Representatives. [In the attached CD: 06 Appendices A-H copy/02 Dear Members of the US HouseofRepresentatives 8_28_2020] Ref 568. and FDA Chief Scientist Hinton removes WRONG time administration for Remdesivir. (Ref 567). MOST AMERICANS DON'T EVEN KNOW OF THIS!	5937026	180874
2020-09-02	FDA removes WRONG time administration for COVID-19 Convalescent Plasma (CCP). (Ref 570). MOST AMERICANS DON'T EVEN KNOW OFTHIS!	6129854	184879
2020-09-16	European Blood Alliance: Support-E European project on COVID-19 convalescent plasma. EU Commission allocates 4M grant for SUPPORT-E. (Ref 581)	6660686	195708
2020-09-25	Pau et al, Ann of Internal Med: This is the NI H's justification of merging Phase I (safety) trials with Phase II (efficacy) trials so as to circumvent completely ever applying PL-115-176: The Right to Try Law with regards to COVID-19 Convalescent Plasma but also any future investigational drug or biologic ad infinatum. This obfuscation by the NIH is tantamount to iustifyin! receated violations of PL-115-176 and is ethically shameful!). (Ref592)	7051336	202732
2020-10-02	President Trump, Rudy Guiliani, Chris Christy, and Ben Carson, M.D. positive for COVID-I9 and are treated with monoclonal Ab or Abcocktail and Remdesivir (Ref 602,603,604,605,606,615,617.618, 620,621,622,626,629,636,640,680,688,689,690,694,705)	7347629	207669
2020-10-07	Eli Li Ily asks FDA for authorization of monoclonal Ab and Regeneron follows with request for monoclonal Ab cocktai I (Ref 61 I, 624, 625,630, 638,639,641,642,643,644,649,651,653,654,655,656,657,658,659,661,664,665,668,671,675,67 677,686,687.	7562786	210779
2020-10-08	lkigcl. ct al: Rcmdcsivir for the treatment of Covid-19 – Final Report. NEJM.org, October 8, 2020. (Ref 613,650)	7620994	211752

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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total U.S.	Total U.S. D
		Cases since	eaths since
Т		1/22/2020	1/22/2020
91-01-020 his sul	Hinton update of Remdesivir EUA. (Ref 627) and again update on 10/22/2020 (Ref 631) the same day the Infectious Diseases division of the FDA gives OK to VEKLURY with a New Drug Authorization (NDA #214787). (Ref 632)	8065129	217721
mission	Hinton update of Remdesivir EUA. (Ref 627) and again update on 10/22/2020 (Ref 631) the same day, Dr JJ Farley, M.D. the Infectious Diseases division of the FDA gives OK to VEKLURY with a New Drug Authorization (NDA #214787). (Ref 632, 633, 634)	8444916	222482
3020-10-31 Signo	Liu, et: Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. Nature Medicine 2020 November. (Ref 646)	9177121	230489
10-11-0 1√for fin	VACO publishes WRONG ILLNESS guidelines for Remdesivir 3 MONTHS after withdrawn by FDA and two weeks after Remdesivir is a prescription drug NDA #214787 . (Ref 647) which is later removed from the Internet tantamount to destruction of Federal Documentation	9255213	230997
60-11-020 ancial	Pfizer announces vaccine. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against	10193449	239251
81-11-0 gain l	Andrus CH: 1 Dear Mr President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. U.S. Copyright Office, 2020-11-18, TXu002232947. (Ref 669)	11619246	251335
out for ed	Simonovich, et al: Arandomized trial of convalescent plasma in Covid-19 Severe Pneumonia, PlasmAR ClinicalTrials.gov number, NCT04383535. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2031304, November 24, 2020, 1-11. (Ref: 679 THIS ŞTUDY WAS RCT GIVEN IN SEVERE COVID-19 WHICH WAS THE WRONG TIME.	12694436	261351
1-20 020-21-020 pcational purpose	Andrus CH: Letter to the Editor of the New England Journa egarding the SARS-CoV-2 virus infection. ***The editor urticle (appropriately age stratified and COVID-19 Convaluiter plasma therapy to prevent severe Covid-19 in older ac 10.1056/NEJMoa2033700, January 6, 2021, 1-9. https://v	16443123	302726
07-71-0000 for ALL the A	Andrus: E-mail submitted to Dr. Richard Stone, M.D., Chief Medical Executive (acting Under Secretary of the Veterans Health Administration), regarding the WRONG INCLUSION CRITERIA which contradicted the FDA directive of early administration in the course of COVID-19 disease (<72 hours from diagnosis) going forward from August 28, 2020 to the present, regarding Remdesivir (an FDA -approved licensed drug: NDA# 214787). This ERRONEOUS DIRECTIVE was still published on the Internet as of October 3, 2021—not having been retracted by the Veterans Health Administration (VHA)—SHAME ON THE VHA! The URL is no longer available. https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf What use to be at this U.S. Department of Veterans Affairs website is the following page that directed the administration of Remdesivir at the wrong time. (Ref 697,	17991925	321791
a2020-12-24	Andrus CH: E-mail directed to the NEJM the VHA, etc. was ignored. (Ref 700)	18827673	333123
70-10-1000 peo	Libster, et al: Early high-titer plasma therapy to prevent severe Covid-19 in older adults, Clinical Trials.gov, NCT04479163. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2033700, January 6, 2021, 1-9. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true (Ref 706). LANDMARK ARTICLE	21553506	366146
a2021-01-12	Regeneron: Regeneron announces U.S. Government agreement to purchase additional COVID-19 antibody cocktail doses. https://investor.regeneron.com/index.php/news-releases/news-release-details/regeneron-announces-us-government-agreement-purchase-additional (Ref 711)	23041951	385821

milestones v case deaths

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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total_U.S. Cases since 1/22/2020	Total_U.SD eaths since 1/22/2020
2021-01-13	Joyner et al: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med, January 13, 2021, at NEJM.org; then republished N Engl J Med 2021; 384:1015-1027. https://www.nejm.org/doi/full/10.1056/NEJMoa2031893 (Ref 713)	23270675	389809
2021-01-21	Eli Lilly announcement to stockholders: Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. https://natap.org/2021/COVID/020321_02.htm (Ref 726)	24821319	415411
2021-01-24	Face the Nation: Margaret Brennan interviews Deborah Birx, M.D. Face the Nation, CBSNews. The abridged version that aired on Face the Nation on Sunday morning, January 24, 2021: https://www.youtube.com/watch?v=odklJGnhvhU (Ref 730)	25329732	424538
2021-02-01	Andrus: Dear Dr. Birx: On March 24, 2020, while there was much discussion and debate about COVID-19 convalescent plasma and the possible development of monoclonal antibodies against COVID-19, U.S. Medicine and the Government failed to explain to the American public the differences and individual utilities of Active Immunization (vaccines to stimulate patient antibody production) and Passive Immunization (provision of convalescent plasmas, convalescence sera, and immunoglobins from other species providing already formed antibodies (IgM, IgG, and IgA) against the virus in COVID-19 immunologically naïve patients immediately within 72 hours of diagnosis (testing positive). (Ref 738)	26485208	448299
2021 02 04	Hinton: EUA-update regarding COVID-19 Convalescent plasma. February 4, 2021 (Ref 740)	26851874	459586
2021-02-04	Trump acquitted of inciting insurrection Ref 761, 762)	27758422	483536
2021-02-13	Promising monoclonal antibodies (Ref 763, 764)	27942629	48727
2021-02-16 2/18/21	Katz LM: (A Little) Clarity on convalescent plasma for Covid-19. Initially published on January 13, 2021) This editorial was republished in the N Engl J Med, 2021 Feb 18; 384 (7): 666 – 668. https://www.nejm.org/doi/full/10.1056/NEJMe2035678 (Ref 770). and FDA revises EUA for COVID-19 Convalescent Plasma. WebMD. John Whyte, M.D., Chief Medical Officer at WebMD interviews Peter Marks, M.D., PhD, Director for the Center for Biologics Evaluation and Research at the U.S. FDA: FDA revises EUA for COVID-19 convalescent plasma. https://www.webmd.com/coronavirus-in-context/video/peter-marks-plasma. (Ref 771)	28083898	492242
2021-02-24	Biden JR: Notice on the Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic. February 24, 2021 – Presidential Actions https://www.whitehouse.gov/briefing-room/presidential-actions/2021/02/24/notice-on-the-continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic/ (Ref 775)	28492480	504565
2021-02-26	The Biden administration buys 100,000 doses of a combination antibody treatment for high-risk Covid-19 patients. The New York Times, Feb 26, 2021. https://www.nytimes.com/2021/02/26/world/bamlanivimab-etesevimab-eli-lilly-monoclonal-antibodies.html	28644508	509110
2021-02-27	NIH halts halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms – Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health announcement is: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-	28715319	51062.
2021-03-08	symptoms (Ref 785). Results upon which discission is based are not released until Nov 18, 2021) Blood center to phase out CCP donations—Due to strong inventory, decline in COVID-19 hospitalization rate, Blood Center will phase out COVID-19 Convalescent Plasma donations March 26, 2021. (Ref 792)	29225673	524042

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calculations owid-covid-data (5).xlsx

Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total U.S.	Total U.S. D
		Cases since	eaths since
Tl		1/22/2020	1/22/2020
81-80-1-03-18 rss submi	Joyner et al: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021 Mar 18; 384 (11): https://www.nejm.org/doi/full/10.1056/nejmoa2031893 and https://www.nejm.org/doi/pdf/10.1056/NEJMoa2031893?articleTools=true (Ref 797)	29786820	536571
05-20-1-03-50 ission	CNN: America's pandemic dead deserve accountability af https://www.cnn.com/2021/03/29/politics/coronavirus-d	30450787	546417
TON 21	Regeneron: Phase 3 Prevention Trial Showed 81% Reduced Risk of Symptomatic SARS-CoV-2 Infections with Subcutaneous Administration of REGEN-COV TM (casirivimab with imdevimab). https://investor.regeneron.com/node/25016/pdf (Ref 811, 812, 813, 814, 815, 838, 858)	31388097	558760
or fina	Casadevall, et al: Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality. eLife 2021; 10e69866.	33462671	592705
52021-08-23	FDA approves first COVID-19 Vaccine (Ref 922)	38101123	626720
07-60-1702 al gai	CDC, COVID-19: Pfizer-BioNTech COVID-19 vaccine overview and safety (also known as COMIRNATY). https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Pfizer-BioNTech.html (Ref 961, 962, 963)	42370019	674301
ont 10-04	NIH: Francis Collins to step down as NIH director by year's end. POLITICO. https://www.politico.com/news/2021/10/04/francis-collins-nih-step-down-515114 (Ref 981, 1064)	43935571	702382
607 educa	Verify 977): Claim that the federal government is rationing monoclonal antibodies. KHOU 11 https://www.khou.com/article/news/verify/verify-federal-government-is-rationing-monoclonal-antibodies/285-aae3608f-c439-4d4f-83de-4e6c76365081 (Ref 988)	44375618	711213
1000 pu	Pfizer: Pfizer's novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in Interim Analysis of Phase 2/3 EPIC-HR study. https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate (Ref 1008)	46503109	752815
8 	SIREN-C3PO Clinical Ref 1022). RESULTS	47583696	767709
61-11-16 for AI	2021-11-18 Kimball S. Biden administration buys \$10 million courses of Pfizer Covid treatment pill in \$5 billion deal. https://www.cnbc.com/2021/11/18/biden-administration-buys-10-million-courses-of-pfizer-covid-treatment-pill.html (Ref 1025)	47709964	769479
12-11-120 12-11-120 12-11-120 13-11-120	Face the Nation: response, CBS News. Fauci says Fauci says he'd be "astounded" if there wasn't an autopsy on what went wrong in COVID response, CBS News. (Attempt of accessing this website on Google: Fauci Brennan Face the Nation on November 22, 2021 was unsuccessful but "autopsy" provided by yahoo): https://www.yahoo.com/now/fauci-says-hed-astounded-wasnt-150638991.html. (Ref1031, 1035, 1036, 1037)	47798634	770202
67-11-130 rican p	Pfizer CEO confident Covid treatment pill will be effective against omicron variant. https://www.cnbc.com/2021/11/29/pfizer-ceo-confident-covid-treatment-pill-effective-against-omicron-variant.html (Ref 1038)	48493302	777915
eople	EDA: FDA expands authorization of two monoclonal antibodies for treatment and post-exposure prevention of COVID-19 to younger pediatric patients, including newborns. U.S. Food and Drug Administration News Release. https://www.fda.gov/news-events/press-announcements/fda-expands-authorization-two-monoclonal-antibodies-treatment-and-post-exposure-prevention-covid-19 (Ref 1047)	49043954	787061

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Thus 22021-12-07	I readment milestones after the 2/1/2020 Entracted	lotal C.S.	lotal U.S. D
		Cases since	eaths since
		1/22/2020	1/22/2020
	WHO: WHO recommends against the use of convalescent plasma to treat COVID-19. December 7, 2021. https://www.who.int/news/item/07-12-2021-who-recommends-against-the-use-of-convalescent-plasma-to-treat-covid-19#:~:text=Convalescent%20plasma%20is%20a%20transfusion.while%20it%20has%20significant%20costs. (Ref 10-51)	49455723	791118
)21-12-16 NIH: https:	NIH: Anti-SARS-CoV-2 Monoclonal Antibodies, Table A. (Last updated 16, 2021) https://www.covid19treatmentguidelines.nih.gov/tables/table-a/ According to the Wayback Machine there are digital copies of	50581783	803656
https: https://display.com/pi.ed/	updates going back to August 6, 2021 with the NIH "last update" is August 4, 2021. https://web.archive.org/web/20210806205833/https://www.covid19treatmentguidelines.nih.gov/tables/table-a/ (Ref 1060, 1069) Fauci: Pfizer's possibly game-changing Covid-19 pill won't be widely available for 'months." https://www.forbes.com/sites/marisadellatto/2021/12/19/fauci-pfizers-possibly-game-changing-covid-19-pill-wont-be-widely-	50946835	806519
availa 021-12-20 Senefi regist	available-for-months/?sh=1bc7e423cc30 (Ref 1066) Senefeld JWf, et al: Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: Anational registry study. PLOS Medicine 2021 December 20; 1-28.	51188108	808071
021-12-22 FDA a	E _	51618251	814170
og 2022-01-07 K Kav applic DEPT.	K Kavanaugh: Miscellaneous Order (12/22/2021) for oral arguments before the U.S. Supreme Court on Friday, January 7, 2022 in application 21A244: NAT. FED'N OF INDEP. BUS., ET AL. V. DEPT. OF LABOR, OSHA, ET AL. and application 21A247: OHIO, ET AL. V. DEPT. OF LABOR, ET AL. https://www.supremecourt.gov/orders/courtorders/122221zr2_f20h.pdf (Ref 1073, 1084, 1087, 1088, 1104	59672311	837409
)22-02-16 Andrus CH (Ref 1131)	Andrus CH: Thank you letter to Gilead Sciences for providing the reference regarding the date of completion of Phase 1 remdesivir trial. (Ref 1131)	78350913	929485
)22-02-22 Trum	Trump praises Putin's 'genius'' incursion into Ukraine (Ref 1132, 1134, 1135, 1136, 1137)	78820149	939160
2022-02-28 Pfizer	Pfizer CANNOT EVEN MENTION Paxlovid's name in advertisement as drug is under an EUA: iSpot.tv: Pfizer, Inc. TV Spot, 'Move Fast: Oral Treatment. https://www.ispot.tv/ad/bAea/pfizer-inc-move-fast-oral-treatment. (Ref 1138, 1146, 1151, 1160, 1179)	79207551	950422
Q2022-03-09 Rubin lottps:	Rubin R: Once viewed as a promising COVID-19 treatment, convalescent plasma falls out of favor. JAMA network https://jamanetwork.com/journals/jama/fullarticle/2790074?guestAccess (Ref 1144)	79561996	963397
)22-05-12 Tin A. https:	Tin A: 1 million COVID deaths: Pandemic's tragic toll in U.S. extends far beyond the numbers. CBS News https://www.cbsnews.com/news/covid-deaths-1-million-us-pandemic-toll/ (Ref 1184)	82479277	1001596
the American people			

milestones v case deaths

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2.0 0.2 2022-09-05 Dear Mr President--Iniquitous Rabbit Holes

150 Emerald Green Ct St. Louis, MO. 63141 September 5, 2022 (revised for submission 9/17-19/2022) Home: (314) 455-9482 Cell of Pam (wife) is 314-809-9634

President Joseph Biden
President of the United States of America
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500
202-456-1414

Re: NIH NIAID Case #12276

Denial of our History has led the U.S.A. down a Series of INIQUITOUS Rabbit Holes

Dear Mr. President:

You and I are anachronisms in our own time for we both assume that the HISTORY of the United States of America and for me, the HISTORY of U.S. Medicine, are important--**BUT** for the present younger generations who wish to ignore, cover over, and who feel betrayed by our HISTORY, it is not! This sense of denial, denigration, and rewriting of HISTORY correlate presently with individual anger and societal intolerance expressed by many today. The disregard for past Medical HISTORY has been and can be presently extremely detrimental with regards to Medical Education and our nation's fight with COVID-19, Monkey Pox, and Polio.

In 1905, George Santayana stated:

Those who cannot remember the past are condemned to repeat it.

Mr. President, you may not initially see the relevance of this letter regarding Medical Education and the Errors in the lack of <u>Immediate TREATMENT of Those who became (and will become) infected with COVID-19</u> over the last two years, BUT it is most relevant to my entire submission to you. Over the last 31 months, there has been <u>NO</u> Organized Direction from U.S. Medicine or the Federal Government in the <u>EARLY (<72 hours from diagnosis)</u>
<u>TREATMENT</u> with immunoglobulins and antivirals for those <u>infected</u> with coronavirus, SARS-CoV-2, COVID-19. While I apologize for this rambling narrative, WHAT FOLLOWS IS VERY NECESSARY.

On September 1st 2022, you gave an outstanding speech on democracy in front of the backdrop of Independence (Constitutional) Hall. https://www.youtube.com/watch?v=F75ZMPRA9QY Your advisors and yourself made the assumption that championing democracy before the physical-foundational epitomization of the origins of Our Democracy would make an impression on the vast majority of the people of the United States. You were wrong! In fact, the major commercial networks ABC, CBS, and NBC chose not to run your speech and instead ran commercial fiction of *Press Your Luck* and reruns of *Young Shelton*, and *Law and Order*, respectively. https://deadline.com/2022/09/joe-biden-speech-primetime-broadcast-networks-1235105916/ You were

outstanding in noting the person who throughout your speech yelled out: F_k Joe Biden, was and is protected by the 1st Amendment to the Constitution. https://nypost.com/2022/09/01/heckler-chants-f-k-joe-biden-throughout-primetime-speech/ The three major news networks omitting your speech in primetime may be *de facto* in violation of their moral mandate to speak, report, and spread truth and decency, but such acts of omission and negating their mandate are protected also by the 1st Amendment. My personal right as an American citizen under the 1st Amendment to the Constitution is to proclaim their omissions of not carrying your speech as reprehensible and admonish them to apologize to you and the American people for abrogating their responsibility as a Free Press guaranteed by the 1st Amendment.

Today, Mr. President, those that cry loudest--right or wrong--hold the stage and are steadfastly intolerant of others questioning their application of their First Amendment rights. Mr. President, you were Constitutionally right in challenging the hackler of your message while still affirming his right to say it:

Americans have often made the greatest progress coming out of some of our darkest moments, like you are hearing in that bullhorn. And then later stating: Good manners is nothing they've ever suffered from.

If today one questions the hecklers of our democracy, one risks their personal indignation and subsequent potential threatening response which is consistent with their interpretation of the 1st Amendment. Abetted by intense digital rhetoric, accusations of a stolen election, and fascist-like threats throughout everyday America, the hecklers of our democracy today have unfortunately instilled fear into all of our hearts. FDR phrased it best in his first inaugural address:

...that the only thing we have to fear is fear itself – nameless, unreasoning, unjustified terror which paralyzes needed efforts to convert retreat into advance.... https://www.archives.gov/education/lessons/fdr-inaugural

Throughout America today, intimidation and the fear of being subjected to *ad hominem* attacks by fellow Americans are all too real. Your intended message last Thursday was unsuccessful in reaching the vast majority of Americans because you chose to confront President Trump on his own turf--a 7th grade narcissistic playground-bully who has seldom, if ever, been corrected in his life nor knows how to apologize. Speaker of the House, Congresswoman Nancy Pelosi, said it best that we need to pray for President Trump while not condoning the lies and incorrect insinuations, incorrect inuendo, and plain meanest he advocates. https://www.youtube.com/watch?v=5yodlvO3Nnk

A Few Examples of how inconsistency or ignorance of history may direct us down the wrong path:

I. Due to England and its colonies adopting the Gregorian calendar (abandoning the Julian calender) in 1752, you and I in our grammar school days reveled in the hope of a holiday from school on February 22nd annually memorializing George Washington's birthday of February 11, 1731, on the Julian calendar https://www.archives.gov/legislative/features/washington#:~:text=George%20Washington%20was%2

<u>Oborn%20in,days%20to%20February%2022%2C%201732</u>. President Washington's chopping down the cherry tree and not lying about it is probably a piece of possible Americana fiction immortalizing Washington's honesty. https://www.nps.gov/articles/george-washington-and-the-cherry-tree.htm. I am sure, there is more truth in this possible American historical falsehood than in any of Mr. Trump's greater than 30,000 lies during the time of his Administration.

https://www.washingtonpost.com/politics/2021/01/24/trumps-false-or-misleading-claims-total-30573-over-four-years/

II. President Gerald Ford pardoned President Nixon over *Watergate* from all criminal prosecution so the country could move ahead which was extremely noble and a necessary step for our country to heal and truly that of an America statesman; but it was political suicide costing him success in his future Presidential run. https://www.jfklibrary.org/about-us/news-and-press/press-releases/profiles-in-courage-for-our-time

Civil ligation around *Watergate* persisted, though, until 1982. Like yourself and all the Presidents since 1982, while in office, President Trump had absolute immunity from civil prosecution because of the U.S. Supreme Court ruling in *Nixon v Fitzgerald* https://supreme.justia.com/cases/federal/us/457/731/. In 1982, in a 5 - 4 decision of the Burger Supreme Court, *Nixon v Fitzgerald*, *457 U.S. 731 (1982)* paved the way for what is occurring today much like the dye was cast by the Taney Supreme Court facilitating the United States' advancement to the Civil War in the *Dred Scott decision* https://www.pbs.org/wgbh/aia/part4/4h2933.html. (Apropos, recently historians have ranked President Trump (2017-2021) second to last before President James Buchanan (1857-1861) https://www.washingtonpost.com/history/2021/06/30/presidential-rankings-2021-cspan-historians/.)

In the majority opinion in *Nixon v Fitzgerald*, two protections from potential abuses by future Presidents of the *Nixon v Fitzgerald* decision were advanced: the Constitutional Imperative of Impeachment and the oversight of the *Free Press*. Throughout his administration and to this very day, President Trump has vociferated against all that is contrary to his perception of his life as "Fake News." Last Thursday by their abrogation of their public mandate to inform the American public in a non-bias way of current events, ABC News, CBS News, and NBC News seemingly failed the entire American public as they *de facto* corroborated and validated Mr. Trump's warped perception and ongoing presentation by not showing-up.

III. Unfortunately, Mr. President, not only did the network channels fail to air your speech, but I do not think you accomplished getting the intent of your Thursday night speech across to the vast majority of Americans in which you restated twice: We the People.... While you and I as children were required to memorize the Preamble to the United States Constitution, the subsequent recent generations have not been compelled regarding such a memorization mandate:

We the People of the United States, in Order to form a more perfect Union, establish Justice, insure domestic Tranquility, provide for the common defense, promote the general

Welfare, and secure the Blessings of Liberty to ourselves and our Posterity, do ordain and establish this Constitution of the United States of America. https://www.archives.gov/founding-docs/constitution

Those of us over age 50 years, were mandated to take history and civics in school which is not as true today. Over the last six years as a VHA physician and surgeon and a University Professor, on Attending rounds (especially on the weekends) I have asked such relevant questions regarding medical education and history as what is the significance of Johns Hopkins University, William Olser, M.D., William Halsted, M.D., Louis Pasteur, Sir Alexander Fleming, Walter Reed, M.D. etc. with responses of universally blank faces of the residents and medical students of Saint Louis University School of Medicine and the Washington University School of Medicine. Over the last year, I have asked the question on rounds where does the expression: We the People... come from? There were usually the same blank stares and most who guessed voiced as the origin of We the People... to be: The Declaration of Independence (although one seemingly insightful student emphatically stated on rounds that, as we were on VA property, We the People... must be a VA saying).

IV. After the establishment of the VA Departments of Medicine and Surgery, PL-79-293 in early January 1946, the subsequent establishment of the VA-University Affiliation by Policy Memorandum No. 2 of January 30, 1946, clearly defines and delimits responsibilities in the VA-University Affiliation:

General Division of Responsibility: The Veterans' Administration retains full responsibility for the care of patients, including professional treatment, and the school of medicine accepts responsibility for all graduate education.

Yet, the mindset of the Universities over the last 76 years in regards to the VA-University Affiliation (Policy Memorandum No. 2) was that of not being limited just to education as is stated in Policy Memorandum No. 2; but, for the last 76 years, the Universities have always attempted to optimize financial profitability from the VA and their ultimate claimed clinical control which is contrary to Policy Memorandum No. 2.

There has been a transition over the last 76 years from the U.S. Government paying the residents assigned to the VA directly--to the present situation in which the VA pays the Universities, so the residents are technically "WOC"--without compensation- and thus not VA employees. Regardless of VA or non-VA Teaching Hospitals, in all states, the residents cannot be licensed for internship and thus are "practicing" as physicians-in-training under the "Teaching Hospital / University" temporary medical license. Subsequent to that first year of residency, each of the fifty state medical licensing boards determine how many years of accredited ACGME residency are required before a physician-in-training can apply for state licensure after completely all the testing steps of the USMLE.

The United States Government through Medicare and the VA is the crucial major funding source for all Resident Medical Education in the United States today. Every

Medicare Part A funded salaried residency position is underwritten with an annual reimbursement of approximately \$110,000 to the "Teaching Hospital" and not the residency program nor the individual resident directly. As the residents' salaries are in the range of \$50,000 to \$60,000 today, benefits count for another ~\$20,000, and malpractice coverage is variable (but most University Hospital programs are self-insured), Medicare Part A resident salary support is a lucrative revenue center for the "Teaching Hospital." As was previously stated, when the residents are assigned to the VA, their salary-line is still funneled through the University, and thus they are not employees of the VA. (The VA makes up about 10% of the Federal Funding of resident salaries.)

United States Medical Education presently is in an <u>unspoken physician-manpower crisis</u> with the graduation of too many MDs and DOs for too few residencies available:

- 1. The Balance Budget Act of 1997 capped the number of residencies that the U.S. Government finances/ supports through Medicare Part A.
- 2. Since the beginning of the new millennia, individual U.S. medical school enrollment has increased, new medical schools are being built, and there has been a net increase in M.D. graduates facing a governmental-financially capped residency system -- all subliminally encouraged by the U.S. Government.
- 3. Osteopathic medical schools have matriculated into mainstream U.S. Medicine over the last two decades so their D.O. graduates are in direct competition with M.D. graduates for ACGME residency positions that are capped by the Balance Budget Act of 1997.
- 4. Success or failure in USMLE I testing of basic science knowledge of the individual medical student are no longer reported to the student or the medical school with a numerically-graduated grade but are just "Pass" / "Fail." Vis-à-vis, residency Program Directors in choosing applicants to interview have only the USMLE II score for initial interview ranking. (Residency interviews have become more about: Who you know, rather than what you know.).
- 5. No medical student nor resident today is aware of the Libby Zion case, New York state's Bell Commission, nor the reason for development of the ACGME "Core Competencies and the subsequent ACGME "Duty Hours." Academic Medicine's responses subliminally resulted in *de facto* blaming "tired" residents as to Academic Medicine's shortcomings. Academic Medicine never admitted to the American people that most "Teaching Hospitals" in the United States had defrauded the American people to some extent by the individual Attending Physicians charges for patient care services under Medicare Part B when the Attending Physician was not present in-person supervising the resident and the resident's salary is being paid for through Medicare Part A. Billing for such services when the Attending Physician is *physically absent* is fraudulent "Double"

- Billing" as the resident salaries are subsidized under Medicare Part A and the E&M or procedural/operative CPT-code reimbursements to the Attending Physicians are under Medicare Part B.
- 6. **Mr. President**, the most tragic thing about this is that from 1996 to 2006, the DHHS and DOJ audited "Teaching Hospitals", published documentation of the fraudulent activities of some of the audit findings on the Internet under Physicians at Teaching Hospitals (PATH) audits, and fined the "Teaching Hospitals" at least ½ billion dollars officially without ever bringing this fraudulent situation to the national consciousness. In short, Academic Medicine hunker downed, paid the fines, developed Compliance Offices at each teaching hospital site, and **NEVER APOLOGIZED TO THE AMERICAN PEOPLE.**
- V. Today, there is LITTLE VESTING required of the resident-physician in caring for the individual patient. Physicians-in-training (residents) are discouraged or even admonished for staying late in the care of a patient due to ACGME Duty-Hour regulations. While Medicine is a Profession, residencies have de facto become shift work apprenticeships with weekly hours capped at 80 hours per week and 4 days off a month are guaranteed regardless if the resident has also taken 1-2 weeks of vacation or sick leave that month. What is worse, while a large majority of residents don't have permanent state licenses and are definitely not on the medical staffs of the teaching hospitals of America, many Attending Teaching Physicians have subliminally abrogated their 24/7 patient care responsibilities/ accountability by permitting the physicians-in-training to "take charge": e.g., the Attending Physicianof-record knowing little of the patient's daily hospital course; the residents may place a patient of another service on "the rounding list" and fail to inform daily the Attending Physician-of-Record the continued in-patient status for days; and when a catastrophic event occurs, (cardiac/respiratory arrest, major change-in-physiology, etc.) the resident fails to notify the attending physician in a timely fashion because, in many instances, the attending physician, his/her department, or the residency program have permissively engendered a sense of not bothering the attending physicians at nights, weekends, or holidays.
- VI. Overall, Mr. President, the idealized imaginary / fictious American doctor who: made house-calls; believed deeply and acted appropriately epitomizing the persona of the doctor-patient relationship; and the physician truly dedicated to each and every presenting patient have gone the way of the Dodo bird. Today, throughout the country, private internists have had their hospital admitting privileges removed so they should no long see daily their established patients of many years in the hospital; and the "hospitalist" and the "acute care / trauma surgeon" typify Academic Medicine which has become shift work with a goal of early discharge. Mr. President, how would you like it if your family or you did not even know the names of the physicians who were caring for you? A hundred years ago, Francis W. Peabody, M.D. both encouraged and admonished physicians https://depts.washington.edu/medhmc/wordpress/wpcontent/uploads/Peabody.html:

... for the secret of the care of the patient is in caring for the patient....

VII. Six years ago when I returned once again as a University Professor of Surgery and VHA Physician and Surgeon, superficially the issues of ghost surgery were resolved in Academic Medicine—(1) in non-VA Teaching Hospitals throughout the nation involving fines and penalties of the PATH audits (~1/4 billion dollars) levied by the DHHS and the DOJ for previous fraudulent activities and threats of continued fines of future DHHS/DOJ audits; and (2) in the VA, by revisions of the VHA Handbook on Resident Supervision (1400.1 and 1400.01) and mandating compliance. My personal perception of the unethical / immoral discriminate, stratified delivery (mainly on financial grounds) of Medical Care to the "haves" versus the "have-nots" remains a persistent undercurrent to this day. What is most distressing is that "medical school" enrollment has become the final prize for all-to-many trainees instead of a pathway for training continued all physicians in a dedication to life-time learning for all physicians. In concert with time (duty hour) limitations imposed by the Liaison Committee for Medicine Education (LCME) and the Accreditation Council for Graduate Medical Education (ACGME), medical education is being directed toward a for-profit proprietary medical school status that was minimized, distained, and discarded by The Flexner Report of 1910 as outlined by Thomas P. Duffy, M.D. in The Flexner Report – 100 Years Later. Yale Journal of Biology and Medicine, vol 84 (2011) pp. 269-276.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3178858/pdf/yjbm 84 3 269.pdf At the turn of the twentieth century, the Flexner Report advocated a medical school based on "the Scientific Method" as Johns Hopkins University of the time. Rigorous analytical studies in the laboratory sciences like: Anatomy, Physiology, Pathology, Microbiology, and Pharmacology were mandated in the primary medical school years with then the progression to clinical years. What exists today is a pervasive medical educational movement to integrate disease topics with the basic sciences into the first two years of medical school emphasizing specific diseases only. While such integration may provide in-depth knowledge of a limited topic, this has been at the detriment of the promotion of personal broad-based foundational development and analytic thinking for the rest of a physician's life. Foundational aspects of the laboratory sciences have become peripheral to the analytical thought process. When I have asked of the medical students in the last six years what basic science texts (or any medical text) they have purchased for their ongoing learning, uniformly the students have stated they have purchased **no textbooks** while in medical school stating they can get all, they will need, on the Internet (in a piecemeal fashion).

A Few Examples of how inconsistency or ignorance of history have directed us down the wrong treatment path with regards to COVID-19 and how treatment paths in future subsequent Infectious Diseases may be influenced:

VIII. Funding of University Research throughout the country is mainly dependent on the Federal Government. Throughout COVID-19, the ever-present risk of losing that funding has become the major impediment to research transparency and honesty with regards to RCTs, placebos, EUAs, etc. by Academic Medicine, the FDA, and the NIH. Individual patient rights to ask for a drug or biologic that are deemed "safe"—in legal terminology, a completed Phase I clinical trial, have been abridged.

Mr. President, during the Trump Administration (and probably your Administration), the Directors or Commissioners were and are well-aware that they have been and are comprehensively violating federal laws! (If you don't believe me, why don't you ask Attorney General Garland, former acting Attorney General Rosen, and former Attorney General Barr for their opinions regarding that which follows.):

- i. On March 13, 2020, DHHS Secretary Azar under his 1135 waiver authority suspended some of the guarantees under EMTALA retroactive to March 1, 2020. The Basic guarantees of EMTALA (Emergency Medical Treatment and Labor Act) are when presenting to an ER anywhere in the U.S.A.:
- 1. Initial stabilization of the patient
- 2. Diagnosis
- 3. Appropriate treatment and disposition

Your administration renewed the waivers in February 2021 and the latest 47-page continuation by your administration was issued on August 18, 2022, https://www.cms.gov/files/document/covid-19-emergency-declaration-waivers.pdf On page 46 of this 47 page document of 8/18/2022, CMS states the following:

Special Waivers

EMTALA:

Only two aspects of the EMTALA requirements can be waived under 1135 Waiver Authority: 1) Transfer of an individual who has not been stabilized, if the transfer arises out of an emergency or, 2) Redirection to another location (offsite alternative screening location) to receive a medical screening exam under a state emergency preparedness or pandemic plan.

For the duration of the COVID-19 national emergency, CMS is waiving the enforcement of section 1867(a) of the Social Security Act

(the Emergency Medical Treatment and Active Labor Act, or EMTALA). This will allow hospitals, psychiatric hospitals, and CAHs to screen patients at a location offsite from the hospital's campus to prevent the spread of COVID-19, in accordance with the state emergency preparedness or pandemic plan.

Mr. President, please read the last two paragraphs regarding EMTALA very carefully. Until the PHE is ended or rescinded by you, Mr. President, the loop-hole regarding accountability of medical personnel (especially physicians) and the hospitals of NOT PROVIDING early treatment (<72 hours from diagnosis) of the disease COVID-19 is "legally" evaded by this obfuscation amounting to Governmental (now your Administration) condoning individual patient abandonment. If one looks closely at the wording, anyone that is screened for COVID-19 "at a location offsite from the hospital's campus to prevent the spread of COVID-19..." de facto has no rights to ask to be seen in a hospital ER and thus has no rights of treatment and disposition under EMTALA.

On March 19, 2020, six days after U.S. DHHS Secretary Azar issued waivers of EMTALA under his 1135 Waiver Authority, the then U.S. Surgeon General Jerome Adams posted this PSA in front of *The White House*: https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/

As the Nation's doctor, I often get asked: What should I do if I think I might have coronavirus? Well, it is important to know the symptoms--they include: fever, cough, and shortness of breath. If you are having these symptoms or worry you might have coronavirus, please call your healthcare provider. We don't want you to go into the ER or the doctor's office without talking to them first because you might spread coronavirus to someone else. They will help you think through and learn how to react including figuring out where to go to get tested if necessary.

Dr. Jerome Adams, PSA, If You Are Sick, March 19, 2020.

Mr. President, as COVID-19 is now going DOWN in the United States from the COVID-19 Epidemic phase to the COVID-19 Endemic phase that will be with us for several centuries, now is the time to officially rescind the Public Health Emergency (PHE) Declaration of March 13, 2020. The Waivers from March 1, 2020

going forward will be terminated. In reading COVID-19 Emergency Declaration Blanket Waivers for Health Care Providers, some of the waivers "will end 151 days after the conclusion of the PHE":

https://www.cms.gov/files/document/covid-19-emergency-declaration-waivers.pdf NO WAIVER WILL BE TERMINATED, THOUGH, UNTIL YOU AS PRESIDENT OF THE UNITED STATES OFFICIALLY CONCLUDE THE PUBLIC HEALTH EMERGENCY (PHE) REGARDING COVID-19.

ii. In 2017, Senate bill S.204 was introduced by Senator Ron Johnson of Wisconsin, as the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina *Right to Try* Act which became Federal Law, PL-115-176 in May 2018. The only stipulation with regards to a patient requesting an experimental drug or biologic off-protocol was that a Phase I Clinical Trial be "COMPLETED."

While the Trump Administration saw PL-115-176 as a shrewd political opportunity without any downside, I would venture that the introduction of the bill in 2017 sent shivers down the spines of all NIH, University, and Pharmaceutical clinical investigators and their patrons. Immediately in 2017 in the medical literature with the FDA and NIH encouraging (not opposing) the merging of the Phases of Clinical Trials, there were several articles suggesting a "seemless phasing" melding Phase 1(safety) and Phase 2 (efficacy) Clinical Trials. This maneuver never mentioned that this would then de facto delay completion of a Phase 1 trial months or years until the Phase 2 study had been completed. Also, by design, a Randomized Controlled Trial (RCT) requires a Placebo control group. In the face of an epidemic with a high mortality and chronic morbidity, recruitment of a placebo group is extremely difficult and probably unethical as coercion is proscribed by the Nuremberg Code, the Helsinki Accords, and the Belmont Report.

Just prior to the Republican National Convention on August 23, 2020, President Trump held a *White House* press conference promoting COVID-19 Convalescent Plasma. https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript (While the transcript still exists, it seems the video of this news conference has been overwritten with the video space-filler: "President Trump Holds a News Conference" https://www.youtube.com/watch?v=nE0EkrElCRk) When Reporter #7 asked specifically regarding availability through the Right to Try Act, President Trump lateralled the response to FDA Commissioner Hahn who did what one of my former mentors would call the "old two step" by circumventing the question and never answering it.

By the way, my former mentor was the first to die in his nursing home in the summer of 2020—I highly doubt he was offered the EARLY administration <72 hours from

diagnosis, as it was, at the time, prohibited by the FDA. The FDA mandated late-inthe-disease administrations were rescinded without any fanfare (nor notification to the American public through the media) for Remdesivir on August 28, 2020, https://web.archive.org/web/20200829175858/https://www.fda.gov/media/137564/download and COVID-19 Convalescent Plasma (CCP) on September 2, 2020. https://web.archive.org/web/20201115054330/https:/www.fda.gov/vaccines-bloodbiologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendationsinvestigational-covid-19-convalescent-plasma). My wife and I stuffed envelops and mailed 537 letters to the U.S. Congress in late August 2020. Mr. President, please see references 559 and 564 of this book specifically in regards to these letters that were sent to Congress (Please see these sections in my submission today: 05 Timeline Bibliography: 20 2022-05-30 annotated Bibliographic Timeline references and the actual letters in 06 Appendices A-H: Appendix C—Copy of letters sent to 537 Congressional offices August 2020). Although I never received any communication from even one of the 537 Congressional offices, in the following weeks, Rear Admiral Hinton, Chief Scientist of the FDA, withdrew the LATE administration mandates and few noticed! In fact, the VA Pharmacy Benefits Management Services, in November 2020, published a sheet on Remdesivir with the **WRONG** administration time (see reference 647). I addressed this incorrect VA policy document regarding on [1] Remdesivir, which on October 22, 2020, had become THE ONLY officially FDA authorized prescription drug in the treatment of COVID-19: NDA #214787, and [2]COVID-19 Convalescent Plasma with VHA Chief Medical Executive Dr. Stone (not Senate confirmed but equivalent to the VHA USH), the FDA, the NIH, and The New England Journal of Medicine. (see references 669, 691, 697, 700, 738, 739, 740, 741, 745, 746, 755, 756, 758, 766, 770, 771). Mr. President, the URL that was the official site of document you see in Reference 647 has subsequently removed and cannot be found.—this is tantamount to the U.S. Government (the U.S. Department of Veterans Affairs) destroying of Official **Government Documentation.**

On March 2, 2021, the NIH <u>canned</u> COVID-19 Convalescent Plasma (ref 785) as a treatment in COVID-19 citing the C3P0 SIREN study NCT04355767 which was a poorly designed, unpowered study overseen by a propriety IRB company that had <u>no</u> Physicians on their board (not a participating University IRB(s) or the FDA which oversees all IRBs). The C3P0 Siren study results were not published until the Fall of 2021, BUT six months earlier were the justification by the FDA and the NIH for the "canning" of COVID-19 Convalescent Plasma: Korley FK, *et.al.*: Early convalescent plasma for high-risk outpatients with Covid-19. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true

Mr. President, as Dr. Francis Collins and Dr. Anthony Fauci still work for the NIH which is an agency of the Executive Branch of the Federal Government and *de facto* you are their boss, I would suggest you ask in person of them to explain the NEJM article to you. I suggest you frankly ask them if this article is valid or, as I have stated, statistically underpowered and unable to be utilized to draw any of the conclusions that have been drawn. In my opinion, this is one of the poorest papers ever published by *The New England Journal of Medicine*.

Mr. President, unfortunately in our litigious, *ad hominem* society today, the Chronology from March 2020 to the present in **05 Timeline Bibliography and 06 Appendices A-H** could be enough to provide the DOJ documentated evidence and a pathway to request the empanelment of a Grand Jury. While that may be true, I do think that more would be accomplished by what I recommend next in **Section IX** to:

- (1) develop an organized plan of a uniform, <u>early</u> treatment (within <72 hours of diagnosis) protocol with immunoglobulins and antivirals in those infected with COVID-19 (regardless of vaccine and booster status);
- (2) develop future protocols for American Medicine to address **novel** viruses where humanity is immunologically naïve.

Mr. President, if you doubt my credibility or my sincerity or have any questions about me, you might wish to have *The White House* Office of General Counsel call some or all of the following individuals below who were my key contacts in my advocacy for Veterans Patients in the fight to remove the open-ended statement in VHA Handbook 1400.1 on Resident Supervision, which *de facto* condoned **Ghost Surgery**:

Level 3: Attending Surgeon not present, immediately available.

As the U.S. Court of Appeals for the Federal Circuit "failed to rule per curiam" in Andrus v VA, Case #03-3162 and there probably have been wrongful veteran patient deaths after the case, I can, if so directed, still appeal to the U.S. Supreme Court on behalf of the Veterans and the American people. The List of some individuals 20 years ago who your OGC might call who were involved in the third book of my submission: 3.0 2022-08-02 VA Resident Supervision book: Dear Mr. President: "...to care for him who shall have borne the battle..." A. Lincoln. are:

Leonard Sistek, former Chief Staffer, U.S. House of Representatives Veteran Affairs Committee

Anthony J. Principi, J.D., former Secretary, U.S. Department of Veterans Affairs Thomas Garthwaite, M.D., former Under Secretary for Health, Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (see references 116, 131, 148)

Richard Griffin, Former VA IG, U.S. Department of Veterans Affairs David Leitch, J.D., former Special Assistant to President Bush Raul Yanes, J.D., formerly in the Office of Counsel to President Bush

Alberto Gonzales, J.D., formerly the Counsel to the President of the United States (President Bush) and later as Attorney General--who Mr. Hernandez, my assigned handler in the DOJ OIG, told me in my last conversation with him: Dr. Andrus, this is our last phone call for the Attorney General personally closed your file.

Jeffery Rosen, J.D., Acting Attorney General of the United States:

December 23, 2020 to January 20, 2021, who most probably knew of me
(although we have never spoken) when he worked in the Office of the Bush
White House Counsel and whose family, over the last 40 years, has exchanged
Seasons Greetings with my family, as Mr. Rosen's wife, Kathy Nichols Rosen,
M.D. and my wife, Pamela Bergkamp Andrus, MA, CCC-SP (314-809-9634)
were undergraduate dorm roommates at Northwestern University. (Believe me,
Pam and I are very proud of Mr. Rosen regarding what he did for Our Nation in
the last month of the Trump Administration and his testimony before the
January 6th Commission).

IX. As Drs. Collins and Fauci are still in the employ of the United States Government (and you're their boss), I truly think they could help heal this country by your requesting of them to direct, collaborate, and produce a medical textbook that they and American Medicine would be proud of. COVID-19: Pathophysiology Testing, Early Treatment, Supportive Care, and Prevention.

I would suggest they include as many as possible the following experts for such a task:

Robert Califf, M.D., the Commissioner of the FDA

Dr. Steven Hahn, M.D. immediate past FDA Commissioner

Peter Marks, M.D., PhD, Director of the Biologics Division of the FDA

Dr. Jay Epstein, M.D., formerly of the Biologics Division of the FDA

Rear Admiral Denise Hinton, R.N., M.S. the former FDA Chief Scientist and now Deputy Surgeon General of the U.S.A.

Vivek H. Murthy, M.D., the U.S. Surgeon General

Dr. Jerome Adams, former U.S. Surgeon General

Dr. Rochelle P. Walensky, M.D., MPH, Director of the CDC

Dr. Robert Redfield, Jr., M.D., immediate past CDC Director

Dr. Ashish Jha, M.D., M.D., MPH, The White House present Covid physician

Dr. Deborah Birx, M.D., former *The White House* Covid physician

Dr. Michael Joyner, M.D., Principal Investigator (PI) of the Mayo Clinic / FDA Expanded Access program for COVID-19 Convalescent Plasma

Arturo Casadevall, M.D., Professor, Internal Medicine, Johns Hopkins University SOM

Liise-anne Pirofski, M.D., Professor, Internal Medicine, Albert Einstein SOM

S. Scott Wright, M.D., Professor, Internal Medicine, Mayo Clinic SOM

Jeffrey P. Henderson, M.D., PhD, Associate Professor of Medicine, Washington University SOM, St. Louis, MO

Bruce Hall, M.D., M.D., PhD, Professor of Surgery, Washington University SOM

Dr. Jacqueline O'Shaughnessy, PhD, Acting Chief Scientist, FDA

The Honorable Xavier Becerra, Secretary, U.S. Department of Health and Human Services

The Honorable Alex Azar, former Secretary, U.S. Department of Health and Human Services.

THE OUTLINE OF SUCH A TEXBOOK SHOULD BE SOMETHING LIKE:

- 1. Pathophysiology of the Coronavirus SARS-CoV-2 (COVID-19)
 - a. Size 80 -120 nm
 - b. Type: RNA coronavirus
 - c. Transmission: mainly respiratory (through the nares and oral inhalation) and possibly by contact of contaminated secretions
 - d. Entry through upper airway and through the attachment to the pneumonocytes of the lungs via the ACE2 receptors of the renin-angiotension-system (RAS)
 - e. Clinical expression:

- i. Early (72 120 hours)—The Viremic Phase: Bilateral pneumonia, headaches, cough, malaise, diminished olfactory sensitivity etc.
- ii. Late (>~120 hours) host immunologic response, multisystem involvement including respiratory deterioration, etc.
 - 1. Cytokine cascade
 - 2. Bradykinin storm
- Outcome: Mortality linearly related in unvaccinated individuals
 (x = age year; y = calculated mortality rate prevalence by age-year):
 - i. 0-45 years of age: y = 0.0008x 0.0103 $R^2 = 0.825$ ii. 46 to >85 years of age: y = 0.0049x - 0.1216 $R^2 = 0.997$
- 2. Clinical Identification:
 - a. Polymerase Chain Reaction (PCR) https://www.ncbi.nlm.nih.gov/probe/docs/techper/ and https://pubmed.ncbi.nlm.nih.gov/21400274/
 - b. Enzyme Linked Immunosorbent Assay https://www.ncbi.nlm.nih.gov/books/NBK555922/
- 3. Isolation, quarantine, masks, etc. (Please note, Mr. President, there is no such thing as an antiviral mask. N95 masks prevent passage of 95% (a 0.95 confidence level—2 standard deviations from the mean) of particles < 300 nm—thus 5% of COVID-19 particles (80 120 nm) can potentially get through by Brownian movement. This is somewhat analogous to a sparrow lighting in a cyclone fence and then flying through. All masks with regards to COVID-19 particles really more-protective to the individuals who come in contact with COVID-19 nares-positive individuals who are wearing masks. In this COVID-19 epidemic, the utilization of Masks epitomized one of the most noble of human attributes to which we aspire: *Do unto others as you would wish them to do unto you*.)
- 4. Therapies:
 - a. Immunotherapies (Passive Immunization—Exogenous Antibodies) (optimum administration within 72-120 hours from diagnosis):
 - i. Polyclonal antibodies: COVID-19 Convalescent Plasma and Sera (These could be available as units or ½ units of convalescent fresh frozen plasma through every blood bank collection service throughout America including the non-for-profit American Red Cross and propriety blood banks like ImpactLife.
 - ii. Monoclonal antibodies and antibody cocktails.(Discussion of development of COVID-19 resistance by Molecular Darwinism):
 - 1. Eli Lilly's Bamlanivimab plus Etesevimab
 - 2. Regeneron's Casirivimab plus Imdevimab
 - 3. GlaxoSmithKline's Sotrovimab
 - 4. Eli Lilly's Bebtelovimab
 - b. Anti-viral agents. (Optimum administration within 72-120 hours from diagnosis)
 - i. IV agents, e.g.: Gilead's VEKLURY: Remdesivir, NDA#214787
 - ii. Oral agents, e.g.: Pfizer's Paxlovid and Merck Sharp & Dome's LAGEVRIO: molnupiravir
 - c. Steroids -- Dexamethasone
 - d. Other
- 5. Prevention:
 - a. Vaccines (Active Immunization—Endogenous Antibodies)

- i. mRNA vaccines: endogenous development of IgM and IgG
- ii. Nasal vaccines: development of IgA
- b. Treatment with Passive Immunization Exogenous Antibodies
 - i. Exposed patients immediate dosing
 - Immunosuppressed patients when weak or no response to mRNA vaccines repeated dosing every 8 weeks of Passive Immunization with repeat dosing intervals dosing with antivirals
 - iii. Monoclonal gammopathies (monoclonal plasma cell tumors) e.g.: multiple myeloma as General Colin Powell had repeated dosing every 8 weeks of Passive Immunization with repeat dosing interval with antivirals
 - iv. Prophylaxis with Passive Immunization in patients with other high risk situations as a bridge until Active Immunization has been acquired
- 6. Supportive Care:
 - a. O₂: Nasal prongs masks ventilators
 - b. Supportive medications: pressors, etc.
- 7. Outcomes:
 - a. Epidemiology:
 - i. Pandemic v Epidemic v Endemic
 - ii. Herd Immunity, what is it?
 - 1. By host disease acquisition
 - 2. By active immunization
 - 3. By passive immunization
 - b. Chronic Outcomes
 - i. Resolution without residuals
 - ii. Long-term COVID-19
 - iii. Chronic morbidities
 - iv. resultant organ failures
 - v. Deaths

Mr. President, before Drs. Fauci and Collins embark on the development of such an organized *Textbook on coronavirus*, *SARS-CoV-2*, *COVID-19*, you probably should ask them to sit down with you and request of them to clarify for you definitions that were distorted throughout the last 31 months and give to you answers to the questions that follow. Mr. President, you should probably request that Dr. Fauci's and Dr. Collin's **Textbook** have an introductory chapter(s) with precisely define terminologies that have been "muddied" in our daily fight against COVID-19 over the last two years:

- a. FDA's Expanded Access or Compassionate Use,
- b. Phase I (safety) Clinical Trials versus Phase II/III (Efficacy) Clinical Trials (Are combined Phase I/II Clinical Trials contradictions to the Intent of The Right to Try PL-115-176 and probably unethical?).
- c. Institutional Review Boards (IRBs),
- d. Conflicts of Interest (especially with regards to BARDA, Operation Warp Speed, etc.),
- e. The fundamental differences between Active Immunization and Passive Immunization
- f. A true medical screening test definition (0.95% confidence level),

- g. Accurate definitions of Sensitivity and Specificity of medical statistics,
- h. Type I and Type II Errors of Medical Statistics and, the failings in our life-time of what Robert Condon, M.D., F.A.C.S. called the "Type III" Error (reference # 76), https://jamanetwork.com/journals/jamasurgery/article-abstract/591890),
- i. Randomized Clinical Trials (RCTs),
- i. Placebos (especially the ethics and appropriateness during an Epidemic),
- k. EMTALA,
- The Right to Try Act (PL-115-176) and how the NIH and FDA have *de facto NULLIFIED* its intent during COVID-19, for orphan diseases such as why it was initially proposed Alzheimer's diasease), and for other such diseases as Amyotrophic Lateral Sclerosis (reference #879: 2021-07-11 Cowen L: Race to a cure for ALS. CBS Sunday Morning, July 11, 2021. https://www.cbs.com/shows/cbs-sunday-morning/video/FTG9i0qA5cvpij a7wvKYtaxvqT4PUtT/race-to-a-cure-for-als/)
- m. EUAs (Emergency Use Authorization) and the difference between an EUA drug or biologic and an FDA authorized drug or biologic as a New Drug Authorization (NDA#), New Molecular Entity (NME) Drug, and a New Biologic Approval.
- The difference between NIH funding and VA Merit funding in regards to <u>direct</u> and indirect funds
- o. Explain the application (contradiction of what has occurred in the last 2+ years regarding disinformation to the American Public by the FDA, the NIH, the PHS, the CDC in what is pointed out in Darrell Huff's classic best seller three-quarters of a century ago: Darrell Huff: *How to Lie with Statistics*. (New York: W.W. Norton and Company, 1954) https://online225.psych.wisc.edu/wp-content/uploads/225-Master/225-UnitPages/Unit-07/Huff StatisticsBook 1954.pdf
- X. What follows are some questions that should outline in your mind the diversity of additional issues that should be address in a comprehensive In the Textbook: COVID-19: Pathophysiology Testing, Early Treatment, Supportive Care, and Prevention:
 - 1. Why did we (the U.S. Government) require, emphasize, and insist on RCTs (Randomized Controlled Trials) during the COVID-19 epidemic over the last two years with placebos when we had thousands, if not millions, of available concurrent matched-control patients infected with the coronavirus, SARS-CoV-2 for all clinical trial studies of biologics and pharmaceuticals in the treatment of the patients who contracted COVID-19? Is the mandate (bordering on coercion) for the use of placebos justifiable and ethical in an epidemic with a disease of a high mortality rate against the backdrop of the Nuremberg Code, the Helsinki Accords, and the Belmont Report? One of the Principal Investigators of the Mayo Clinic/FDA Expanded Access Protocol answered a reporter's question in the following manner on August 12, 2020, which probably should be denounced by every IRB in the country (ref: 543):

Since April, the Trump administration has set aside **more than \$300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving highrisk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

Kozlov M: Two Washington U. doctors lead national effort to study new COVID-19 treatment. St. Louis Post-Dispatch Aug 12, 2020. https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article_ccec0f56-4493-5a26-8601-45e35d364b2d.html

- 2. Dr. Fauci, why did you <u>not</u> object when Dr. Schleifer, in your presence, on March 2, 2020, incorrectly defined *Passive Immunization* as Passive Vaccination and by verbal slight-of-hand <u>did not discuss</u> polyclonal antibodies at the meeting? This inhibited (actually did not bring up even the possibility of) discussion of possible mobilizing of the American Blood Banks (i.e.: coordinated by the American Red Cross) in plasma drives to collect in an organized fashion, process, and distribute COVID-19 Convalescent Plasma to be administered within 72 hours of contraction/diagnosis in individuals infected with coronavirus, SARS-CoV-2?
- 3. Why were blood bankers, the American Red Cross, and rank-and-file clinicians not invited to the meeting of March 2, 2020?
- 4. Why was Dr. Peter Marks, Director of FDA Biologics, not forthcoming regarding the early (<72 hours) administration of COVID-19 Convalescent Plasma?
- 5. Rear Admiral Hinton, while you issued the histories and advocacies for early administration of the antiviral Remdesivir and COVID-19
 Convalescent Plasma beginning in late August 2020, as you wrote about this in your continued issuance of EUAs, why did the FDA fail to **emphasize** these histories with U.S. Medicine, the Congress and the President, and the American people?
- 6. Mr. President, Ask Drs. Collins, Fauci, and Califf to help you understand the definitions and fuzzy thinking that occurred regarding:
 - a. Safety (Phase I) clinical trials and Efficacy (Phase II/III) clinical trials
 - b. Implementation (non-existence) of the Right to Try Act of 2018, PL-115-176
 - c. Expanded Access (Compassionate Use) and how data from Expanded Access cannot be used in the completion of a Phase I study

- d. Mr. President, why, after you received the antiviral Paxlovid twice daily for five days, did you had difficulty pronouncing its name in your post-infection News Conference? (hint: Paxlovid's name is was new to you and Paxlovid's name is not known to the American public. Why?--because the FDA, the FCC, and the FTC would probably fine Pfizer if its name were mentioned on the Pfizer's cartoon advertisements on television. https://www.ispot.tv/ad/bAea/pfizer-inc-move-fast-oral-treatment Paxlovid is still experimental under EUA 105 https://www.fda.gov/media/155049/download, while Remdesivir (VEKLURY) is the **ONLY antiviral** authorized by the FDA in the treatment of COVID-19 as an intravenous prescription drug (NDA#214787) since October 22, 2020. https://www.cbsnews.com/news/covid-19-paxlovid-pill-monoclonalantibodies-treatments/ Under FCC, FTC, and FDA guidelines, Pfizer advertising an experimental drug by name (Paxlovid) in deference to a prescription drug (Veklury) is probably illegal. In short, Gilead Pharmaceuticals could sue Pfizer for advertising Paxlovid in deference to the omission by the FDA of the approved competitor drug: Remdesivir.
 - i. **By the way Mr. President**, your administration has purchased 20 million boxes of the 5-day units of dosages of Paxlovid for the Test and Treat program (See ref. 1138).
 - ii. Why has the FDA and the NIH consistently (sometimes on a daily basis), electronically-overwritten documents without outlining or distinguishing the corrections so as to *de facto* prevent the scrutiny of the American public and the PRESS?
 - iii. Drs. Collins and Fauci, the Anthrax-in-the-mail terrorist attacks on the Eastern seaboard in 2001 were contained and resolved over the course of about 2 months. At the time, the U.S. Government was worried about the potential weaponization of smallpox as a terrorist agent in the future. So, the U.S. PHS came up with a plan on vaccinating medical personal and first responders against smallpox? Why didn't they proceed with these inoculations across the country? (Several medical personnel in their 50s or above who had been

vaccinated as children against smallpox with attenuated varicella virus and, in 2002, had tested negative for smallpox antibodies were given a smallpox vaccine, developed pericarditis, and died. See references 128, 192)

Since the label on the vial

https://www.google.com/search?q=monkeypox+smallpox+vaccine &source=lnms&tbm=isch&sa=X&ved=2ahUKEwiImp6TlaH6Ah WwkYkEHQcvDNoQ AUoAnoECAEQBA&biw=698&bih=675 &dpr=2#imgrc=zfqj2DD_SKQXeM in the treatment of monkey pox today includes "smallpox", is there a risk for pericarditis in those who were vaccinated as children for small pox? Also, are the older generations of Americans today NOT virus-naïve as they were vaccinated against small pox as children? The present vials of vaccine are labelled Monkey Pox Small Pox

https://www.cdc.gov/poxvirus/monkeypox/files/interim-considerations/guidance-jynneos-prep-admin-alt-dosing.pdf

I do realize that the small pox vaccine of the 18th century that Edward Jenner used is not the same *Vaccinia* strain. There are two vaccines being used today: JYUNNEOS

https://www.cdc.gov/poxvirus/monkeypox/files/interim-considerations/guidance-jynneos-prep-admin-alt-dosing.pdf and Acam 2000 https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/acam2000-vaccine.html

(Please note that myocarditis and pericarditis have been reported in the mRNA vaccines against COVID-19. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html)

- e. Since Regeneron Pharmaceutical's monoclonal cocktail was effective for about a year until the fall of 2021 when SARS-Cov-2 developed resistance to the Regeneron monoclonal cocktail, why hasn't Regeneron Pharmaceutical investigated and promoted a subsequent monoclonal cocktail as *Eli Lilly* has done. Dr. Schliefer pointed out that Regeneron had at least a 1000 isolated antibodies on March 2, 2020?

 https://www.youtube.com/watch?v=31i6p_stzW8
- f. Could the FDA and the NIH organize a public conference to invite and educate the entire nation:

- i. on how to correct aberrancies that occurred over the last two years in regards to the definitions that have been muddied and misapplied;
- ii. alleged violations of individual American rights with the suspension of EMTALA and the disregard for AND non-application of the Right to Try Act of 2018, PL 115-176;
- iii. disregard for immunotherapy (an *de facto* rationing) before the general public in those who are infected with COVID-19;
- iv. disregard for the FDA approved prescription antiviral drug for COVID-19: Remdesivir (VELKURY), NDA# 214787; and
- v. the CONTINUED administration of millions of doses of vaccines, antivirals, immunoglobulins, and biologics still as experimental drugs (EUA) even though they could be declared by the FDA no longer experimental –but rather prescription therapeutics?

Mr. President, please excuse what seems to be wanderings without an organized purpose. I started this letter by stating that you and I are anachronisms in our time. American history—no matter the topic—has been for you and I an integral part of our daily education and expansion of our foundational knowledge in all aspects of our history. While ignorance may be blissful transiently, all too often, we may traverse life down the wrong rabbit hole if we construct a house-of-cards without solid historical foundation.

This present submission was initiated by the fact that VA retirement people cannot locate my existence at the Edward Hines, Jr. VAH as Chief of Surgery (1996-2002) of the tertiary VAMC in the Chicago area to appropriately calculate my pension which requires the averaging of my three highest consecutive annual salaries. I officially have been *misplaced or lost* (i.e.: my Official Personnel File (OPF) cannot be located in the VA or the U.S. National Archives, and thus, **I have become an "unperson" from 1982 to 2002**.) There seems to be no accountable person in the U.S. Department of Veterans Affairs or the Veterans Health Administration who can direct the search for my existence as Chief of Surgery of the Edward Hines, Jr. VAH. In 1946, the Edward Hines, Jr. VAH was the original site of the U.S. Government's approved agreement between Paul Magnuson, M.D., F.A.C.S. and Charles Puestow, M.D., F.A.C.S. for introducing University (Northwestern University and the University of Illinois) faculty and surgery residents into the daily care of Veteran patients in Building 1 of the Edward Hines, Jr. VAH in Maywood, Illinois! Mr. President, did you know that the Hines VAH historically was not only the origin of the VA-University Affiliation (VA Policy Memorandum No. 2, January 30, 1946) but also had an airstrip on the property that Charles Lindbergh, whose hometown was

St. Louis, MO, would every-other-day fly the air mail from an airstrip in St. Louis to the airstrip at the Hines VAH, Chicago? While this cover letter has been arduous for you to read, my informing you of all contained in today's submission is my duty, as a Physician and Surgeon of the Veterans Health Administration of the U.S. Department of Veterans Affairs, to the people of the United States of America and to you as their President. Like all federal employees of the Executive Branch of the Federal Government, I serve at the pleasure of the President of the United States of America. While I am not one of your personal advisors and just a VA Physician and Surgeon, I ask your permission to suggest the following that you could initiate for the betterment of all the Departments, Agencies, Commissions, etc. of the Executive Branch of the U.S. Federal Government:

- 1. **Mr. President**, please consider writing an Executive Order to promote greater transparency in all non-classified Executive Branch documents, handbooks, policies, memos, etc. by ordering the following:
 - a. **STOP** all changes or destruction of Executive Branch Website URLs on official U.S. Government websites;
 - b. **STOP** all electronic <u>overwriting</u> of all non-classified Executive Branch documents, handbooks, policies, memos, etc. without documenting for future viewing and electronic access previously rescinded documents, etc. of the Executive Branch of the U.S. Government; and
 - c. **ASK** of each agency to reconstruct the electronic pathways to all non-classified previously-overwritten documents or those websites where the URLs have been changed.
- 2. **Mr. President,** consider suspending the concept of privatization of the Executive Branch of the Federal Government or at least in the VA. (e.g.: the St. Louis VAMC employs a private firm to verify all third party billings—at least 70% of all E & M and procedural CPT code billings at present are rejected.)
- 3. **Mr. President,** while the EUAs were useful during the early part of the COVID-19 U.S.A. epidemic, after so many doses have been given out safely and most of the drugs and biologics have demonstrated some efficacy, do you think the FDA could assign the antivirals and biologics permanent NDA#s so that a Medical Textbook like *COVID-19: Pathophysiology Testing, Early Treatment, Supportive Care, and Prevention* could be more definitive, more straight forward, and provide an organized, uniform approach to physicians, hospitals, and medical schools throughout the United States of America.

Mr. President, thank you for your taking the time to have reviewed my submission.

Respectfully,

Charles H. Andrus, M.D., F.A.C.

Physician and Surgeon, Surgical Service, John Cochran VAH, St. Louis VAMC, St. Louis, MO

Cc:

Catherine Mitrano, J.D., and Michael R. Hogan, J.D. Office of General Counsel (26)
Designated Agency Ethics Official (DAEO)
810 Vermont Ave, N.W.
Washington, D.C. 20420
Phone: 202-360-2598

Re: NIH NIAID Case #12276

Anthony S. Fauci, M.D.

Director of the U.S. National Institute of Allergy and Infectious Diseases

U.S. National Institutes of Health

U.S. Department of Health & Human Services

5601 Fishers Lane, MSC. 9806

Bethesda, MD 20892-9806

Phone: 301-496-5717 (last varified July 2020) FAX: 301-402-3573 (last varified July 2020)

Re: NIH NIAID Case #12276

The Honorable Denis McDonough Secretary, U.S. Department of Veterans Affairs 810 Vermont Ave, NW Washington, D.C. 20420 Denis.McDough@va.gov

Re: NIH NIAID Case #12276

Abigail Carlson, M.D.
Centers for Diseases Control/DDID/NCEZID/DHQP/OD
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Re: NIH NIAID Case #12276

Kara Harris, MPH

Section Chief for Controlled Correspondence and Public Inquires Legislative Affairs and Correspondence Management Branch Office of Communications and Government Relations

U.S. National Institute of Allergy and Infectious Diseases

U.S. National Institutes of Health

U.S. Department of Health & Human Services 5601 Fishers Lane, MSC. 9806, Room 6F30

Bethesda, MD 20892-9806 Kara.Harris@nih.hhs.gov

Phone: 240-627-3693

Re: NIH NIAID Case #12276

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3.0 0.3 2022-8-31 Dear Mr President submission coverletter.pdf

150 Emerald Green Ct St. Louis, MO. 63141 September 1, 2022 (314) 455-9482

President Joseph Biden
President of the United States of America
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500
202-456-1414

Re: NIH NIAID Case #12276

Dear Mr. President:

Several weeks ago after you had been treated for COVID-19-positivity documented in screening by a nasal swab/testing and treated with Paxlovid, in a press conference you fumbled over the pronunciation of Paxlovid which is the Pfizer oral antiviral most effective if given early within three to five days of diagnosis. Your administration has bought millions of doses of Paxlovid to be distributed in some 40,000 pharmacies throughout the United States—free to the American people in your Test-to-Treat Initiative (as Pfizer cannot commercially sell Paxlovid to the American public as it is under an Emergency Use Authorization (EUA) and thus experimental. While Paxlovid has recently gained some notoriety due to Mrs. Biden's and your successful treatment, you would think more people would know of it. You'd be wrong! In the Midwest, most people don't even know it exists; and they don't realize they should take it immediately after the diagnosis of COVID-19 regardless of their vaccine status, regardless of their booster status, or regardless of the presence (or absence) of any potentially life-threatening, concomitant morbidities like diabetes, hypertension, age, immunosuppression, obesity, etc. In short, Mr. President, you fumbled on the pronunciation of Paxlovid because it isn't a household name. For that matter, in Pfizer's advertisements on television, the company is not permitted to advertise Paxlovid's name as that is probably illegal! Why is it illegal?—because the FTC does not allow promotion of an experimental drug in deference to a legally authorized drug approved by the FDA: since October 22, 2020, Veklury (Remdesivir) has been designation specifically by the FDA as an intravenous prescription drug in the treatment of COVID-19: FDA NDA #214787. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf Mr. President, please go to the hyperlinks of this letter using the data card I have submitted to you and watch the short cartoon advertisement of Paxlovid and related FDA documentation. https://www.ispot.tv/ad/bAea/pfizer-inc-move-fast-oral-treatment; EUA 105 regarding Pfizer's nirmatrelvir/ritonavir (Paxlovid): https://www.fda.gov/media/155049/download; and EUA 108 regarding Merck Sharp & Dome's molnupiravir (Lagevrio) https://www.fda.gov/media/155053/download

Mr. President, the FDA, the NIH, the VA, etc. have been (1) derelict in their duty to the American people and (2) have misinformed the American public enabling greater than 1,000,000

deaths from coronavirus SARS-CoV-2 virus (COVID-19). How did this happen? The index misdirection occurrence took place in *The White House* on March 2, 2020, when Dr. Leonard S. Schleifer, M.D., PhD, co-founder and CEO of Regeneron Pharmaceuticals responded to President Trump's question regarding the difference between vaccines and monoclonal antibodies with a inaccurate misdirection (WHICH WAS WRONG FUNDIMENTALLY) coining the phrase: *Passive Vaccination* – There is no such thing! https://www.youtube.com/watch?v=31i6p_stzW8 (Mr. President, I would suggest that you have an aide review the entire 58 minutes and report to you as to who also was present in the room [and most notably who was missing like representatives of the Association of American Blood Banks (AABB) including the American Red Cross] and did not object to this incorrect phraseology: https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus)

Mr. President, the textbook definitions are:

- 1) Active Immunization (endogenous immunotherapy: vaccination)
- 2) Passive Immunization (<u>exogenous</u> immunotherapy: polyclonal antibodies (COVID-19 Convalescent Plasma or Serum, monoclonal antibodies or biclonal antibodies). By NOT TREATING EARLY (< 72 HOURS) during the <u>viremic phase</u> and by RATIONING stupidly in the administration only to the severely ill in the late phases of the coronavirus, SARS-CoV-2 virus (COVID-19) during the <u>cytokine cascade</u> and <u>bradykinin storm</u>, and have lied to the American people.

HOW DID THIS HAPPEN?—very simply, Mr. President, all the Departments and Divisions of the Executive Branch of the Federal Government that dealt with COVID-19, the Congress, and the President went along with the misdirections, de facto rationing, de facto cover-ups, and lies taking the American people down the Rabbit Hole by (1) incomplete explanations; (2) making previous policies, directives, and handbooks difficult to find or discover due to URL changes, misdirections, or deletions; or (3) perpetuating the Federal Government status quo practice of electronic overwriting thus making previously rescinded documents extremely difficult to locate and/or complete removal (vis-à-vis destruction of governmental documentation) from the Internet! Over the last two years, the FDA, the NIH, and other divisions of the Department of Health and Human Services (DHHS) have played word salad with definitions, have ignored their own stated policies, and have overlooked, purposely misinterpreted, and violated the intent of federal laws, e.g.:

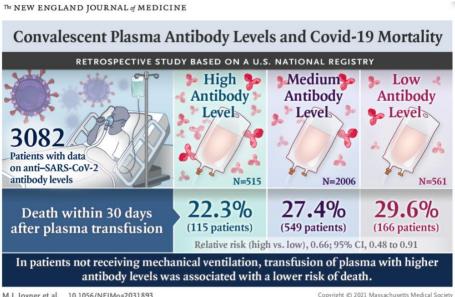
- 1. The FDA seldom, if ever, declared a Phase 1 (Safety) Clinical Trial completed; and the NIH created and encouraged "seamless" Phase 1 / 2 (Safety/Efficacy Combined) Clinical Trials so a Clinical Trial would never have to be declared completed. This was a direct governmental evasion of the intent of The Right to Try Act: PL-155-176 and is tantamount to legal obfuscation / abridgement of every man, woman, and child's right under PL-155-176.
- 2. Definitions have purposefully been misinterpreted:
 - a. **Compassionate use** of an experimental drug or biologic cannot be used in evaluations or conclusions of Clinical Trials. The World Health Organization and

the U.S. Institute of Medicine warned the United States of America in 2014 regarding the use of convalescent plasma in the treatment of Ebola. The most notorious example to date is of the Mayo Clinic / FDA Expanded Access protocol. In FDA terminology, **Expanded Access** equals **Compassionate Use** which means that the >94,000 units of COVID-19 Convalescent Plasma (CCP) utilized from April 4, 2020 until August 23, 2020, were not and cannot be used officially to declare "safe for human use" and thus completing a Phase 1 clinical trial.

b. All the publications from the Mayo Clinic / FDA group directed by Michael Joyner, M.D. have reported that **CCP is safe** but, as it was administered under the title of **Expanded Access**, the results cannot be used to declare any of the NIH Clinical Trials like the Mayo Clinic / FDA protocol an officially-completed Phase 1 (safety) Clinical Trial. Mr. President, please glance at **Attachment 1** of this letter outlines Dr. Joyner's frustration with the FDA. As Dr. Joyner responded in an e-mail in July 2020 to Dr. Kevin Behrns, M.D., F.A.C.S., co-editor-in-chief of the medical journal *Surgery* and, at the time with me, the other General Surgeon, Department of Surgery, Saint Louis University School of Medicine (SLUSOM): "*Having a lot of trouble with USG*."

Dr. Behrns asked me what this statement meant. I chuckled and explained that <u>USG</u> meant <u>United States Government</u>. Yep, the FDA and the NIH had really screwed-up! Through the Mayo Clinic/FDA protocol, they had given (1) CCP as a Compassionate Use-only-biologic (Expanded Access) thus precluding reporting officially concluding results from the NIH NCT04338360 and (2), the CCP had been given at the **wrong-time (at death's door)** during the cytokine cascade and the bradykinin storm instead of the early viremic phase when it would have been most effective.

Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, Verdun NC, Marks P, van Buskirk CM, Winters JL, Stubbs JR, Rea FR, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather D, Wright RS, Casadevall A, *et. al.*: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med, January 13, 2021, at NEJM.org; then republished N Engl J Med 2021; 384:1015-1027. https://www.nejm.org/doi/full/10.1056/NEJMoa2031893



M.J. Joyner et al. 10.1056/NEJMoa2031893

Conclusions

Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was associated levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.

- c. Mr. President, by August 2020, I had submitted to Dr. Fauci's office two analyses in the use of CCP which per the office of Ms. Kara M. Harris, MPH, have been included in NIH NIAID Case # 12276. (I also submitted them to the U.S. Copyright Office of the U.S. Library of Congress to preserve for history--See Attachment II.) I would think that you, like every other person in the world, could make a formal FOIA request of the FOIA officer of the NIH NIAID for a copy of my submission(s) with a processing fee of somewhere between \$5 to \$20.—For your convenience, this cover letter which I am submitting to you today is part of the hard-copy documentation and digital compendium on the attached SanDisk Ultra Plus SDHA UHS-1 Card so your office need not request the information under the FOIA. (I do apologize for this seemingly ironic/sarcastic statement, but for the last 40 years as a VA physician and surgeon, I am thankful to the U.S. Department of Veterans Affairs has focused me on how to create a paper trail so as to document for history controversies that have arisen.)
- 3. While there a many other definitions, policies, etc. that are discussed within that which I have submitted of which this is a summary cover letter. Much of what went wrong throughout the Trump Administration in dealing with COVID-19 was due to President Trump's interpretation, exploitation, and abuse of Nixon v Fitzgerald 457 U.S. 731 (1982) https://supreme.justia.com/cases/federal/us/457/731/ which was the U.S. Supreme Court ruling and opinion that for the last 40 years has assured the President of the United States of America absolute immunity from civil litigation. In the opinion of the Court, there were two protections: Impeachment and the Press. Well, President

Trump was impeached and acquitted twice—the 2nd acquittal was in regards to one article of impeachment alleging he incited the insurrection on January 6, 2021. As all Americans are protected by the double jeopardy clause of Amendment V of the U.S. Constitution, President Trump realistically cannot be tried again for his involvement in January 6, 2021, and all his subordinates can claim they served at the "Pleasure of the President." From the start, President Trump made frequent *ad hominem* attacks against individual reporters and the free press at large thus rendering the free Press impotent in the eyes of his supporters. A legal flanking maneuver by the FBI, the DOJ, and Attorney General Garland focusing on the Trump Machine--as was performed by the FBI and the Postal Inspectors against Al Capone—is in the process; but such will be opposed by a incessant legal obfuscation and public misdirection.

Mr. President, a quarter of a century ago, as was my duty, I naïvely thought that, as a VHA physician and surgeon, I could advocate successfully for Veteran patients by objecting through the EEOC, the MSPB, and the U.S. Court of Appeals for the Federal Circuit in Andrus v VA Case #03- to reduce or—more appropriately--completely end Ghost Surgery (Attending Surgeons not physically present in the OR) within the VA-University affiliation (PL- and Policy Memorandum No. 2). While VHA Handbook 1400.1, Resident Supervision, has subsequently been revised multiple times over the last two decades, this has been accomplished by of changing of the VHA Handbook URL in changing the title from 1400.1 to 1400.01 and by electronic overwriting rendering previous versions non-discoverable. As I was so threatening to VA "Good ol' Boys Club" mindset regarding Attending Surgeon supervisory responsibilities, I returned to VA service at the St. Louis VAMC in August 2016 as a "new hire" at a Grade 15, Step 7 when I had separated from the VA in January 2002 at a rank of Grade 15, Step 10. Over the last six years, I have been told by personnel of the St. Louis VAMC H.R. that my Official Personnel File (OPF) covering 1982 to 2002 cannot be found in the U.S. National Archives. At present time, the VA retirement people have not be able to verify my existence at the Edward Hines, Jr. VAH even though I was (1) the Chief of Surgery from 1996-2002; the "redacted" VA OIG Combined Assessment Program of the Edward Hines, Jr. VAH, report No. 99-00173-18 of November 22, 1999 https://web.archive.org/web/20080917181921/https://www.va.gov/oig/cap/99-00173-18.pdf , documents my existence as my name was not redated from the cover letter of Appendix IV (pages 43-44) regarding my Excel data base recordings of Attending Surgeon Supervision of Hines VAH Surgery residents requested by the VA OIG in October 1999--the 17 pages that follow (pages 45-61); and on December 10, 1999, along with Drs. Bowen, Garthwaite, Petzel, and Roswell, I was interviewed for the position of VHA Under Secretary for Health by the USH Commission chaired by retired Mississippi Congressman Gillespie V. "Sonny" Montgomery in the VACO 10th floor conference across from The White House. Mr. President knowing the uniqueness of the Federal Government, I will bet you a six-pack of diet Coca-Cola that when my back pay is adjudicated by the VA, a lump sum payout plus my annual salary or pension may exceed your annual salary. What that will mean is that another division of the Federal Government will garnish this payout that exceeds \$400,000 in one year.

Mr. President, after 25 years of physically functioning as a VA physician and surgeon, the range of appropriateness to incorrectness never surprises me. For approximately four to five days in late January 1982, the daily transport of patient meals over 17 miles was disrupted from the Jefferson Barracks (JB) division (chronic neurology-psychiatric-rehab-nursing home site) of the

St. Louis VAMC) to the John Cochran (JC) division (acute medicine / surgery site) of the St. Louis VA due to an unexpected blizzard. Although I cannot verify it, I was told at the time that there is a Congressional mandate that when there are two divisions of one VA hospital, there can be only one patient kitchen. So, since the construction of John Cochran VA Hospital (JC) in 1950 to the present, all patient meals are cooked at JB. There are plans to build a new hospital tower at JC and on the drawings is roughed-in dietary facilities. I expect that if those proposed JC facilities contain a new patient kitchen, then the food for the JB patients will probably be transported daily from JC for the next 70+ years.

As a young Attending Surgeon at JC in the 1980s, I was asked by the Chief of Prosthetics if I could arrange his presentation to the Attending Physicians and Residents from Washington University SOM and Saint Louis University SOM. On a subsequent Friday afternoon at three o'clock in the John Cochran VAH OR conference room, the VA Chief opened with: 1 veteran patient, 1 amputation, 1 prothesis. I raised my hand and asked what that meant. The VA Chief informed all that it was federal law that if a Veteran Patient's protheses broke due to wear-and-tear, he would have to pay out of personal funds to fix it or replace it for the VA was prohibited from doing so. I exclaimed: "That is the stupidest thing I have ever heard." Unflustered, the VA Chief matter-of-factly responded: "The VA is like the Mississippi River—you got to go with the flow."

Blindly following any concept, policy, directive, or statute is humanly inconceivable and, when it hurts or adversely affects another, unconscionable. A quarter of century ago I tried and somewhat succeeded in minimizing Ghost Surgery in the VHA by advocating for the muting of the misinterpretation, misapplication, and potentially - inherent, abusive abandonment of VA patients in the interpretation of VHA 1400.1: Level 3: Attending surgeon not present, but *immediately available*. Over the last two decades, with changing the title of the VA policy from 1400.1 to 1400.01, changing the URL, and by electronic overwriting, no operating room case (except initially in a life-or-death situation) will start with surgery residents in the absence of the Attending Surgeon-of-Record preop progress note and without the documented level of Attending Surgeon resident supervision during the case. This came at personal costs to my family and myself: (1) the threat of financial insolvency due the loss of my VA job, (2) in Andrus v VA, docket # 03-3162 the U.S. Court of Appeals for the Federal Circuit per curiam "failed to rule", and (3) the VA retirement people can't seem to find documentation of my existence as the Chief of Surgery of the tertiary VA hospital of the Chicago area from 1996-2002—I am literally am what George Orwell referred to in his book entitled: 1984 as an *Unperson* in the VHA.

While the VHA has muted the mindset of Attending Surgeon supervision from afar and the U.S. Departments of Health and Human Services and Justice forced the curtailment of the practice through the **Physician at Teaching Hospital** (PATH) audits from 1996 through 2006 exacting at least a quarter of a billion dollars from the Teaching Hospitals of the U.S.A. in fines and penalties, *de facto* lack of vesting in each individual patient and *de facto* individual patient abandonment by shift work through the Internal Medicine Hospitalist and Acute Care Surgery system is pervasive in each teaching hospital in the nation. While the Libby Zion case, the Bell Commission, and ACGME Duty Hours have established daily duty time limits so that individual patient tragedies are hopefully minimized, academic and organized Medicine have inadvertently

become parties to an ongoing system of medical educational mediocrity and lack of encouragement of physician-patient vesting. In the last six years of my tenure as a VA General Surgeon, Surgical Service, John Cochran (St. Louis) VAMC and Professor of Surgery, Department of Surgery, Saint Louis University SOM, when questioned, not a single medical student has responded that any of them have purchased any textbooks in Medical School for the basic science years nor for any clinical clerkships. Their fundamental base knowledge in any topic is limited at best relying on piecemeal case reports integrated with unorganized divergent bits of *Evidence Based Medicine*! The residents and students do not know the significance of Johns Hopkins University in Medical Education nor even in which city it is located; and they definitely don't know who William Olser, M.D. nor William Halsted, M.D. were. None of them know nor understand the significance of the Flexner Report of over a century ago which eliminated approximately 600 propriety medical schools and non-scientific apprenticeships / trade schools pervasive of that day.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3178858/pdf/yjbm_84_3_269.pdf Mr. President, do you want physicians carrying for you family practicing shift-work Medicine who have never read a medical textbook? I sure don't!

In our response to COVID-19, Physicians of America should be ashamed as we all should be versed in the history, concepts, and application of Clinical Immunology in the treatment of noval viruses! American Medicine have allowed political fighting and back-biting, self-promotion, and the goal of individual financial gain to drive the overall Medical response in the treatment of COVID-19! Every Internal Medicine textbook for a specific disease like COVID-19 should contain a summary chapter for each specific disease like COVID-19. What follows is my own very oversimplified outline.

Mr. President, Drs. Collins and Fauci are still federal employees, and you are their and my bosswhy not ask them to pen a monograph on the Pathophysiology and Treatment of Coronavirus, SARS-CoV-2 that will counter that which exists today before the public eye? Dr. Fauci, Dr. Collins, myself, and you, Mr. President, all grew-up in the new age of television exposed for a decade to weekly viewing of GE College Bowl. While, Mr. President, I'm only a practicing General Surgeon, and they, being research medical clinicians, are most qualified in the topics of virology, molecular biology, and infectious diseases, yet as a clinically-based physician and surgeon seeing patients daily for a half of a century, I challenge Drs. Fauci and Collins to a public debate. Knowing that today we can't do anything without legal advice, you could offer to Drs. Fauci and Collins the opportunity to have the Office of General Counsel attorneys of the DHHS be present. For my legal counsel, I request of you to consider asking Jeffrey Rosen, J.D., former acting Attorney General of the United States (December 23, 2020 to January 20, 2021) to assist me in my oral auguments. Mr. Rosen was the Edmund Ross (Profiles in Courage) of our time and is worthy of the *Profile in Courage* award from the Kennedy foundation. Mr. Rosen is a staunch Republican lawyer in federal public service for at least a quarter of a century in the Office of the Counsel to President George W. Bush and, most recently, various attorney positions within the Executive Branch of the Trump Administration culminating in his Senate appointment as U.S. DOJ Deputy Attorney General and subsequent acting Attorney General of the United States from December 23, 2020 to January 20, 2021. I am a Physician and Surgeon (Democrat) who has worked within the University-VA Affiliation of the Veterans Health Administration, off-and-on, for 40 years. I have medically/surgically provided healthcare for

every Veteran Patient that presented for General Surgery care before me. While Mr. Rosen and I have nothing publicly in common and we have never met, my wife, Pamela Bergkamp Andrus, CCC-SLP, closely followed the encounters between President Trump and the DOJ during in December 2020 and January 20, 2021. She constantly reiterated that Jeff is a good guy and we should be really proud of him in his dedication to duty as the Acting Attorney General of the U.S.A. Yes, we followed the events closely for my wife, Pam, has had some personal insight into Mr. Rosen in the past as she was the undergraduate roommate at Northwestern University of Jeff's wife, Kathleen Nichols Rosen, M.D. In short, Mr. President, I truly believe Mr. Rosen and I could counter the physicians and attorneys of the DHHS and DVA for the betterment of all Americans in a debate regarding the clinical addressing of COVID-19 in a GE College Bowl format. Below is a possible, suggested, abbreviated version of a monograph review, a textbook chapter, or a in a debate format regarding Coronovirus, SARS-CoV-2 and therapy based on the pathophysiology of the disease COVID-19.

- 1. Pathophysiology of the Coronavirus SARS-CoV-2 (COVID-19)
 - a. Size 80 -120 nm
 - b. Type: RNA coronavirus
 - c. Transmission: mainly respiratory (through the nares and oral inhalation) and possibly by contact of contaminated secretions
 - d. Entry through upper airway and through the attachment to the pneumonocytes of the lungs via the ACE2 receptors of the renin-angiotension-system (RAS)
 - e. Clinical expression:
 - i. Early (72 120 hours)—The Viremic Phase: Bilateral pneumonia, headaches, cough, malaise, diminished olfactory sensitivity etc.
 - ii. Late (> ~120 hours) host immunologic response, multisystem involvement including respiratory deterioration, etc.
 - 1. Cytokine cascade
 - 2. Bradykinin storm
 - f. Outcome: Mortality linearly related in unvaccinated individuals $(x = age\ year;\ y = calculated\ mortality\ rate\ prevalence\ by\ age-year)$:

i.	0-45 years of age:	y = 0.0008x - 0.0103	$R^2 = 0.825$
ii.	46 to >85 years of age:	y = 0.0049x - 0.1216	$R^2 = 0.997$

2. Clinical Identification:

- a. Polymerase Chain Reaction (PCR) https://www.ncbi.nlm.nih.gov/probe/docs/techpcr/ and https://pubmed.ncbi.nlm.nih.gov/21400274/
- b. Enzyme Linked Immunosorbent Assay https://www.ncbi.nlm.nih.gov/books/NBK555922/
- 3. Isolation, quarantine, masks, etc. (Please note, Mr. President, there is no such thing as an antiviral mask. N95 masks prevent passage of 95% (a 0.95 confidence level—2 standard deviations from the mean) of particles < 300 nm—thus 5% of COVID-19 particles (80 120 nm) can potentially get through by Brownian movement. This is somewhat analogous to a sparrow lighting in a cyclone fence and then flying through. All masks with regards to COVID-19 particles really more-protective to the individuals who come in contact with COVID-19 nares-positive individuals who are wearing masks. In this COVID-19 epidemic, the utilization of Masks epitomized one of the most noble of human attributes to which we aspire: *Do unto others as you would wish them to do unto you*.)

4. Therapies:

- a. Immunotherapies (Passive Immunization—Exogenous Antibodies) (optimum administration within 72-120 hours from diagnosis):
 - i. Polyclonal antibodies: COVID-19 Convalescent Plasma and Sera (These could be available as units or ½ units of convalescent fresh frozen plasma through every blood bank collection service throughout America including the non-for-profit American Red Cross and propriety blood banks like ImpactLife.
 - ii. Monoclonal antibodies and antibody cocktails.

 (Discussion of development of COVID-19 resistence by Molecular Darwinism):
 - 1. Eli Lilly's Bamlanivimab plus Etesevimab
 - 2. Regeneron's Casirivimab plus Imdevimab
 - 3. GlaxoSmithKline's Sotrovimab
 - 4. Eli Lilly's Bebtelovimab
- b. Anti-viral agents. (optimum administration within 72-120 hours from diagnosis)
 - i. IV agents, e.g.: Gilead's VEKLURY: Remdesivir, NDA#214787
 - ii. Oral agents, e.g.: Pfizer's Paxlovid and Merck Sharp & Dome's LAGEVRIO: molnupiravir
- c. Steroids -- Dexamethasone
- d. Other

5. Prevention:

- a. Vaccines (Active Immunization—Endogenous Antibodies)
 - i. mRNA vaccines: endogenous development of IgM and IgG
 - ii. Nasal vaccines: development of IgA
- b. Treatment with Passive Immunization Exogenous Antibodies
 - i. Exposed patients immediate dosing
 - ii. Immunosuppressed patients when weak or no response to mRNA vaccines
 repeated dosing every 8 weeks of Passive Immunization with repeat dosing intervals dosing with antivirals
 - iii. Monoclonal gammopathies (monoclonal plasma cell tumors) e.g.: multiple myeloma as General Colin Powell had repeated dosing every 8 weeks of Passive Immunization with repeat dosing interval with antivirals
 - iv. Prophylaxis with Passive Immunization in patients with other high risk situations as a bridge until Active Immunization has been acquired

- 6. Supportive Care:
 - a. O₂: Nasal prongs masks ventilators
 - b. Supportive medications: pressors, etc.
- 7. Outcomes:
 - a. Epidemiology:
 - i. Pandemic v Epidemic v Endemic
 - ii. Herd Immunity, what is it?
 - 1. By host disease acquisition
 - 2. By active immunization
 - 3. By passive immunization
 - b. Chronic Outcomes
 - i. Resolution without residuals
 - ii. Long-term COVID-19
 - iii. Chronic morbidities
 - iv. resultant organ failures
 - v. Deaths

Mr. President, your speech last night from Philadelphia focused on the continued fight for the soul of this nation. https://www.youtube.com/watch?v=JemWkV2Vcic [transcript: https://www.whitehouse.gov/briefing-room/speeches-remarks/2022/09/01/remarks-by-president-bidenon-the-continued-battle-for-the-soul-of-the-nation/]. You summarized your pivotal role in this continued fight for democracy:

But I'm an American President — not the President of red America or blue America, but of all America.

And I believe it is my duty — my duty to level with you, to tell the truth no matter how difficult, no matter how painful.

Mr. President, I have submitted this plea to you today because you are the moral leader of this nation. We are a country of laws. When agencies like the FDA, the NIH, and the VHA avoid their own policies, directives, or memorandum, they are being inconsistent with their mandate to the American people. James Cardinal Gibbons, Archbishop of the Baltimore diocese and backdoor advisor to five of the Presidents of the United States stated in 1909:

Reform must come from within, not from without. You cannot legislate for virtue.

I apologize for the amount of documentation; but through this documentation, I hope to suggest some concrete strategies consistent with your noble plea of September 1, 2022:

1. Over my 40 years being connected with the Executive Branch of the Federal Government as a VA physician, we have gone from hard-copy policy and directive documents that list

on the factsheet the previous rescinded document so one can find it and compare/contrast the two documents regarding equivalence and where they differ. Today, with electronic overwriting and changing URLs, such identification of previous documents and their errors within are non-discoverable—**THIS IS CONTRARY TO GOVERNMENTAL TRANSPARENCY** which is so important in a representative democracy. In many ways, that is what happened during COVID-19 as the FDA, NIH, CDC, etc. overwrote daily publications without any justification. The foundational tenants of Infectious Disease Medicine on how to address a novel virus have not changed with regards to Passive Immunization in over the last 140 years. Yet, from *the March 2, 2020 White House* meeting () onward, the NIH and the FDA provided the American public a hodge-podge of conflicting paths where research and medical care were driven by financial self-motivation at many levels. Mr. President, you are the boss of the Executive Branch of the Federal Government which includes all the agencies (e.g.: FDA, NIH, CDC, PHS, BARDA, etc) of the U.S. Department of Health and Human Services.

- a. I would suggest your meet with all Cabinet Secretaries and their Under Secretaries and request that they develop strategies for all branches of the Executive Branch of the Federal Government not to destroy documentation by electronic overwriting and thus become more transparent because changing URLs and electronic overwriting in the Federal Government is de facto destruction of documentation and, if known to the American public, would be illegal. The URLs of all previously rescinded documents should be unique and no electronic overwriting permitted. As has been for a quarter of a century, the only way to find an overwritten previous document is to search with the Internet Archive's Wayback Machine [https://archive.org/web/] hoping that sometime in the past the Internet Archive (a non-governmental, not-for-profit digital archival library located at 300 Funston Ave., San Francisco, CA) has digitally stored the specific searched-for-document. If the URL of a specific document has been modified (even by one character) at all, then the document becomes non-discoverable/digitally lost. If the contents within an URL have been erased or the URL changed, so too the document becomes non-discoverable representing destruction of documentation. Mr. President, I am sure vou could issue an Executive Order: (1) to stop all destruction of federal URLs going forward, (2) to stop all electronic overwriting without providing the electronic location of the overwritten document going forward, and (3) have every agency in the Executive Branch of the Federal Government resurrect / reconstitute/ reconstruct all pathways to every previous hard-copy version of the present digital documents from the digitization of the Federal Government approximately 25 years ago. The uniform response from all agencies will be that those documents are on Digital Server Farms so they can be found in future litigation BUT that the documents are not readily discoverable for every American which is non-transparency before the American public.
- b. Simply put, B.A.R.D.A. (Biomedical Advanced Research and Development Authority) of the U.S. DHHS should NOT be directing Medical Research—only facilitating financing directed by the NIH, NSF, FDA, CDC, etc. (e.g., Regeneron

Pharmaceuticals was given over a half a billion dollars in early 2020 to develop antibodies against the coronavirus, SARS-CoV-2. Its CEO on March 2, 2020 reported that Regeneron had isolated ~1000 antibodies to COVID-19. Regeneron chose two antibodies to construct a cocktail (Casirivimab plus Imdevimab) which was given to President Trump IV four hours after he turned positive in October 2020) made billions from the government, produced a monoclonal antibody cocktail that worked until COVID-19 mutated

- c. The FDA and the NIH should stop avoiding the implementation of Right to Try Act PL-115-176
- 2. hey have obstructed the the implementation add the right trip try act of 2018 and that's collectively denied Americans their rights to ask for any experimental drug once phase one trials (safety—which requires Dad at the wrong time what a bunch stop we all want **NOT EFFICACY**)

a.

3. sss

Attachment I: 2016-08-09 Behrns KE: *Curriculum vitae* of Kevin E. Behrns, M.D., F.A.C.S., co-editor-in-chief of *Surgery*. https://com-surgery-main.sites.medinfo.ufl.edu/files/2016/08/View-Kevin-Behrns-curriculum-vitae.pdf

In July 2020, Dr. Behrns was a General Surgeon of the Department of Surgery, Saint Louis University School of Medicine; co-Editor-in-Chief of *Surgery*; and was a fellow faculty member in General Surgery Division, Department of Surgery, Saint Louis University School of Medicine of Saint Louis University and shared the General Surgery outpatient offices with me on Friday mornings. Knowing that he had graduated from the Mayo Clinic Medical School and had been a Surgery resident and researcher at the Mayo Clinic in the 1990's, I requested of him that he contact Michael Joyner, M.D., the Principal Investigator for the Mayo Clinic / FDA Expanded Access program for COVID-19 Convalescent Plasma. Dr. Joyner responded with a brief e-mail response to Dr. Behrns:

Having a lot of trouble with USG.

By that time in July 2020, I had submitted to the offices of Dr. Fauci, Dr. Hahn, and President Trump multiple communications regarding *Passive Immunization treatment* with COVID-19 Convalescent Plasma which had been included in my submissions 1.) to the U.S. Copyright Office to be preserved for history in the Library of Congress and 2.) had been included in NIH NIAID case #12276:

- Andrus CH: *Time*: The Crucial *Independent* Variable of the COVID-19 Pandemic, U.S. Copyright Office, Library of Congress, 2020-06-08, Txu002199029.
 <a href="https://web.archive.org/web/20210904014401/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=9&ti=1%2C9&Search_Arg=Andrus+Charles+H&Search_Code=NALL&CNT=25&PID=DvTGOW_Qvd_foYxTFrVcdewL3ktMCwz&SEQ=20210425193720&SID=1
- 2. Andrus CH: The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma. U.S. Copyright Office, 2020-07-22, TXu002214049.

 <a href="https://web.archive.org/web/20210904020833/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=6&ti=1%2C6&Search_Arg=andrus+charles+h&Search_Code=NALL&CNT=25&PID=cXfFuGrmHQvLVlLvfNNt7Yjwh73ImgQ&SEO=20210512081428&SID=1

Dear Mr. President, please note that all information I have submitted over the last two years to Dr. Fauci was directed by Dr. Fauci to be dealt with by:

Kara M. Harris, MPH
Section Chief for Controlled Correspondence and Public Inquires
Legislative Affairs and Correspondence Management Branch
Office of Communications and Governmental Relations
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Per her letter of June 10, 2020, Ms. Harris assigned my correspondence with Dr. Fauci's office to NIAID Case #12276 and I have continued to submit my correspondence addressed with Dr. Fauci's office for the last two years labelled in the heading: NIAID Case#12276. After reviewing Dr. Fauci's White House slide show on Monoclonal Antibodies of August 24, 2021, 10:30 to 15:27 minutes on the URL, I called Ms. Harris's office on 8/30/2021 leaving a message requesting that Dr. Fauci call me.

529) 2021-08-24 Zients J, Walensky R, Fauci A, Murthy V: Press briefing by White House COVID-19 response team and public health officials. Transcript: https://www.whitehouse.gov/briefing-room/press-briefings/2021/08/24/press-briefing-by-whitehouse-covid-19-response-team-and-public-health-officials-51/

YouTube (Fauci slide show: 10:22 – 15:27 minutes in presentation) https://www.youtube.com/watch?v=AZNP05w2cxU

In a phone response to my phone call (my VA office phone number is: 314-652-4100 ext 54463), "Meg" who identified herself from Ms. Harris's office responding for their office stated that all the information I had submitted had been forwarded to the appropriate divisions. I then pleaded my case with "Meg" who patiently listened for about twenty minutes. Finally, when she stated she needed to go, she stated in her parting comments that she assured me that they still had all the information I had submitted in NIAID Case #12276. Thus, under the Freedom of Information Act (FOIA), all in NIAID Case #12276 should be available to anyone properly requesting it under Federal Law.

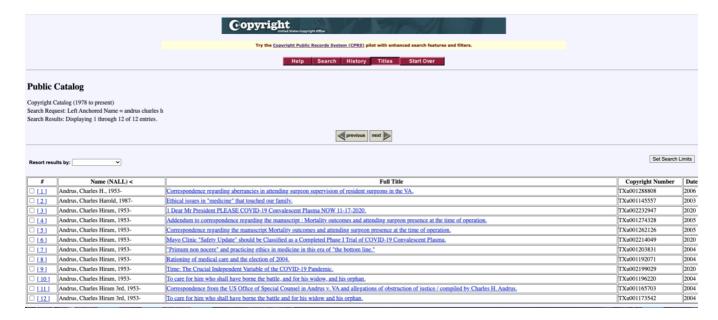
Mr. President, please excuse my digressing from Dr. Joyner's e-mail response to Dr. Behrns of: Having a lot of trouble with USG. Mr. President, could you please excuse the 'expletives' (E!) that I will include in my discussion that follows because over the course of the last two years the American people (and the World) have been misled, misinformed, and lied to (E!) regarding major issues of treatment of COVID0=19 by agencies of the Federal Government (e.g., FDA, NIH, CDC, PHS, VA, etc.), spokespersons of Organized / Academic Medicine (e.g.: *The New England Journal of Medicine*), and the Biological and Pharmaceutical industries assisted by B.A.R.D.A., other research agencies like DARPA, etc.

After Dr. Behrns voiced Dr. Joyner's e-mail response of "having a lot of trouble with USG", Dr. Behrns questioned me as to who was USG? My response was simple: USG is the United States Government; and Dr. Joyner was referring off-handedly to a nebulous but responsible/accountable USG. I then explained that the USG had so screwed up (E!) that "they" didn't know how to get out of the rabbit hole.

 2016-09-27 U.S. Federal Register: Clinical Trials Registration and Results Information Submission. A Rule by the Health and Human Services Department on 09/21/206. Phase I meaning in 21 CFR 312.21. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-B/section-312.21

Attachment 2:

My submissions to the U.S. Copyright Office of the Library of Congress regarding Ghost Surgery in the VA (9 submissions) and regarding COVID-19 (3 Submissions)



Attachment #3: Outline just some of the mistakes made with origin on March 2, 2020, in *The White House* where the available treatment of polyclonal antibodies, COVID-19 Convalescent Plasma was ignored.

Mr. President,

Please excuse these volumes of documentation that I have sent to you and the outspoken, unsolicited, forwardness of my appeal to you personally, but our national therapeutic response to COVID-19 has been tantamount to the U.S.P.H.S.'s Tuskegee Syphilis project of four decades in the mid-twentieth century. August 23rd 2020, was the second anniversary of the theoreticallyincreased-availability of COVID-19 convalescent plasma (polyclonal antibodies) for the entire American public. President Trump used the Press Conference on the evening of August 23rd 2020, before the start of the Republican National Convention to demonstrate himself "presidential" in his concern for all Americans regarding the use of the tried and true treatment methodology of *Passive Immunization (convalescent plasma and serum)* of the last 135 years. Passive Immunization has been utilized in the initial treatment for many disease-entities for which Karl von Bering was awarded the first Noble Prize in Medicine and Physiology and Medicine and has one of its origins in Louis Pasteur's rabies-treatment of Joseph Meister, a nine year-old boy with extensive dog bites from a rabid dog in 1885. Convalescent plasma and sera have been used successfully in in the multitude of maladies and prevention of subsequent medical conditions: rabies; hydrops fetalis (Rhogam); tetanus-prone wounds (Hypertet); treatment of novel viruses when vaccines did not exist; treatment of bacteria when antibiotics were unknown and unavailable; in small pox in newly, unvaccinated, diagnosed cases and contacts; insect and snake envenomations; etc. Between April 4, 2020 and August 23, 2020, through the FDA/Mayo Clinic expanded access (compassionate use only) protocol greater than 94,000 units of convalescent plasma were administered late, at the **wrong late administration** time (>72 hours). The wrong-time administration protocol was quietly removed from all subsequent EUAs by the FDA Chief Scientist, Denise Hinton, R.N., M.S., who at present is the Deputy Surgeon General of the United States—but for months later, the practice was wrongly continued **LATE** as the VHA initiated in November 2020 (Attachment A). With regards to President Trump's gambit, it backfired.—Researchers and physicians of Academic/University Medicine pounced and declared COVID-19 Convalescent Plasma was probably not very useful. Instead of making COVID-19 Convalescent Plasma more available to be given within the first 72 hours of diagnosis or symptomatology, it has been and was **WRONGLY** administered late (>72 hours) in the disease during the phases of cytokine cascade and bradykinin storm in which no antibody therapy (including vaccine) would be very effective in the aggregate when used at death's door. This medical stupidity was promoted by academic medicine and federal medicine (FDA, NIH, CDC, PHS, BARDA...) resulting in over a million preventable deaths. In short, this was analogous to a Tuskegee syphilis project "mindset" which was wrongly promoted, wrongly implemented, and wrongly applied across the nation.

Attached to this cover letter are 15 letters that I wrote to you since the start of your administration that I never sent as they each addressed separate distinct errors in medical statistics, medical definitions and terminology, administration of appropriate therapeutics, and outright abandonment by the FDA, NIH, University Research Medicine, etc.—in short, it was like the Indian parable: *The blind men and the elephant* which in 1873 the American poet John

Godfrey Saxe transformed into a poem. Also attached on the data card is a chronologic reference bibliography of over 1187 references regarding COVID-19 justifying every statement I have made in this cover letter:

<u>2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where</u> we went wrong > 05 Timeline Bibliography > **10** 2022-05-30 Bibliographic Timeline <u>References</u>

--- and also on the attached data card is a more complete parallel annotated bibliography with quotes, analysis, and relevance linkage:

<u>2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where</u> we went wrong > 05 Timeline Bibliography > **20** 2022-05-30 annotated Bibliographic Timeline References .

Instigated by announcements publicly of four unrecognized medical errors publicly in March 2020, America has therapeutically gone ignorantly down-the-rabbit-hole:

- 1. March 2, 2020: In a *White House* conference https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus of President Trump, Vice-President Pence, physicians of the Executive Branch of the U.S. Federal Government, and Physicians and CEO's of the Pharmaceutical Industry, Dr. Leonard Scheifler, M.D., PhD, CEO of Regeneron Pharmaceuticals, https://www.youtube.com/watch?v=31i6p_stzW8 incorrectly answered President Trump's inquiry about the difference of vaccines vs monoclonal antibodies by explaining *Passive Vaccination* (which is a misnomer) and does NOT exit:
 - a. Active Immunization: Vaccination with Antigens IM which require 14 days for the development of IgG against COVID-19. (Mr. President, the reason your wife and you, have recently tested positive is that you, like all "vaccinated Americans" were not vaccinated with a nasal spray so as to develop IgA.—so, while your symptoms were muted by two primary IM vaccinations and two boosters that stimulated endogenous IgM and IgG, you never produced IgA in you nares until your recent infection.)
 - b. Passive Immunization: Immunoglobulins administered EARLY (<72 hours):
 - i. COVID-19 Convalescent Plasma (CCP) which is cheap, safe, and readily available through the collection, testing, and processing by the Blood Banks of America (Early administration of CCP was ignored at that March 2, 2020 meeting as neither representatives of the AABB (Association of American Blood Banks) nor the America Red Cross were invited to the table.)
 - ii. Monoclonal Antibodies and Antibody cocktails which are expensive, safe, and but are subject to COVID-19 developing resistance as they are only

one or two antibodies and **NOT** polyclonal antibodies like COVID-19 Convalescent Plasma.

- 2. March 13, 2022: U.S. DHHS Secretary Alex Azar announced http://www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx the suspension of parts of EMTALA retroactive to March 1, 2020 thus negating / abridging *de facto* the rights of all Americans.—Tantamount to *de facto* medical martial law which exists even today in 2022. Essentially, no one can ask for early treatment with the Early Administration (<72 hours from diagnosis / symptomatology) of COVID-19 Convalescent Plasma (or immunoglobulins) and the initially, when it became available (May 1, 2020) the intravenous antiviral, Remdesivir, which since October 22, 2020, has been a prescription drug, FDA NDA #214787, in the treatment of COVID-19 that can be prescribed by any M.D. or D.O. legally in all 50 states, D.C., and other sites of the U.S.A. that could be infused for 3 5 days, twice a day, early (<72 96 hours) in the course of the individual patient's COVID-19 for Every Man, Woman, and Child that had and will contract SARS-CoV-2 (COVID-19).
- 3. March 18, 2020: U.S. PHS Surgeon General Adams advised in a PSA to all Americans NOT to go to the hospital if they were possibly sick with COVID-19 which *de facto* abandoned Every Man, Woman, and Child that had and will contract SARS-CoV-2 (COVID-19). https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/
- 4. March 24, 2020: The FDA announced **INCORRECT** inclusion criteria for the administration of COVID-19 Convalescent Plasma (and subsequently all therapies pervasive to this day, September 3, 2022):

2020-03-24 U.S. Food and Drug Administration: Investigational COVID-19 Convalescent Plasma – Emergency INDs, March 24, 2020.

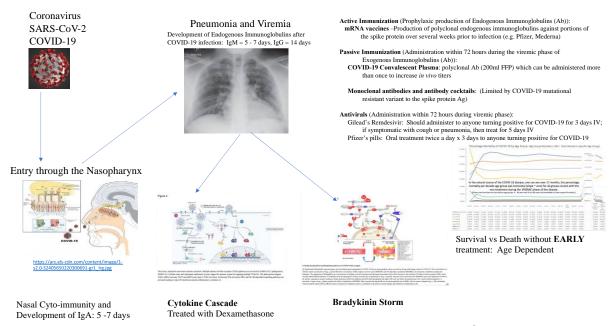
https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20 %20FDA.pdf

based on an **INCORRECT** interpretation of an epidemiology article from Wuhan China published one month before in the Journal of the American Medical Association online on February 24, 2020:

Wu Z, McGoogan JM: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) Outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. Doi:10:1001/jama.2020.2648. https://jamanetwork.com/journals/jama/fullarticle/2762130

After reading this cover letter, the 15 accompanying letters, and other pertinent documentation, Mr. President, you can confirm that which I'm saying to you by calling on Anthony Fauci, M.D. and Francis Collins, M.D. Ask of them, as <u>you are our boss of the Executive Branch of the Federal Government</u>, to write a monograph for you explaining the pathophysiology of COVID-19 convalescent plasma and the initiation of appropriate **early administration of immunoglobulins and antivirals** in the treatment of a novel virus like SARS-CoV-2 (COVID-19) universally for all! If you wish, I, as a VHA physician and surgeon, will construct for you,

Mr. President, a much-needed clinically-focused "chapter" for the **individual patient** for a medical textbook on the pathophysiology of SARS-Cov-2, testing, prevention methods and vaccination, early therapeutics in those COVID-19 infected (<72 hours) with immunoglobulins and antivirals, and supportive treatment late in the disease (>72-96 hours). The attachment below is a diagrammatic representation of COVID-19 pathophysiology.:



1.002 2022-02-27 Pathophysiology and treatment of Covid-19

Mr. President, how has the widespread COVID-19 tragedy of the morbidities and mortalities in America been augmented and facilitated our present societal mindset? -- we have *de facto* substituted for our motto: *In God We Trust* with that of which we faulted the Communists during the Cold War: *The end justifies the means*. The Communist rhetoric was proclaimed by the U.S.A. during the Cold War as *Propaganda*. Mr. President, did you know that the word *Propaganda* comes from the root phase "to propagate" as epitomized by the name of the missionary society of the Catholic Church: *The Society for the Propagation of the Faith*?

A half a century ago, President Gerald Ford probably lost his election bid to continue as President of the United States because he put the country's well-being above his own political solvency by pardoning President Richard Nixon from criminal culpability with regards to *Watergate*. Unfortunately, while all criminal prosecution was immediately curtailed and the pardon helped America heal, lawyers around the country had the mindset that they could still sue the President of the United States in civil litigation. In 1982, the Brennan Supreme Court ruled in a 5-4 decision in favor of President Nixon in *Nixon v Fitzgerald*. This decision is the reason why all subsequent Presidents have had **absolute immunity** from all civil litigation. Before and throughout President Trump's four years in office, he abused this ruling by lying to the American public over 30,000 times. In the opinion of the Brennan Court, there were two safeguards that would prevent or diminish such abuse: (1) the Constitutional imperative of Impeachment of the President of the United States for "high crimes and misdemeanors" and the *de facto* oversight by

the Press. As the amoral businessman President Trump has been throughout his life and seemingly 7th grade playground bully, he persists, even to this day, with *ad hominem* attacks on any person that opposes his agenda which is his (as is every American's) right under the First Amendment. **Therefore, every time the Press attempted to responsibly report the news contrary to President Trump mindset, he declared and discredited it as** *FAKE NEWS***. The intent of First Amendment was not to promote nor guarantee irresponsible behavior, though, as "***crying FIRE***" in a theater, etc. What is more, while the January 6th Commission of the U.S. House of Representatives is correctly chipping away at President Trump's façade, by his Senatorial acquittal in his second Impeachment Trial, President Trump is protected from any future prosecution regarding his involvement in the January 6th, 2021 insurrection by the Constitutional prohibition of double jeopardy afforded to all by the Fifth Amendment. In short, the Republican Senators provided President Trump with a forever Get out of Jail card!**

If, as I state, the compendium of attached documentation regarding American Medicine's response to COVID-19 was a BIG medical mistake, what's in it for Federal and Academic Medicine and Research? In 2018, President Trump signed into law PL-115-176: TRICKETT WENDLER, FRANK MONGIELLO, JORDAN MCLINN, AND MATTHEW BELLINA RIGHT TO TRY ACT OF 2017. Per PL-115-176, the right of every American to ask for any experimental (under an EUA) drug or biologic is absolute and is guaranteed provided a Phase I Trial (a Safety Study) has been *completed*. – For the Medical Researcher, Clinical Grant Awardee, and the Universities, Pharmaceutical Companies, and the Medical Device Manufacturers, the status quo of medical research in the United States must irreparably change by PL-115-176. So, what has the FDA and NIH done?--they have failed to declare any therapies in the treatment COVID-19 officially "safe" and have merged the concepts of "safety—Phase I clinical trials" with "efficacy—Phase II-III clinical trials" thus de facto proscribing the application and circumventing the intent of PL-155-176--even when there is appropriate scientific proof of the safety of COVID-19 Convalescent Plasma (polyclonal antibodies) reported in over 94,000 doses that were wrongly administrations late in the pathology of the disease in individual Americans.

Mr. President, why don't you ask Drs. Fauci and Collins: Why has early administration (within 72-96 hours of symptomatology or diagnosis) of COVID-19 Convalescent Plasma (CCP), other Immoglobulin agents, and antiviral agents not been nationally advocated nor universally announced for all Americans? COVID-19 Convalescent Plasma (CCP) has been available since the start of the American epidemic in March 2020. It can easily be collected and processed by the blood banks of America (both private, propriety blood banks, and those administered by the American Red Cross). Every hospital and outpatient infusion center in the nation could and should have administered a one-time dose (or more if it is "low dose") through outpatient and inpatient infusion centers across the nation. Like that which occurred during WWII when the first director of the American blood drive, Charles Drew, M.D., F.A.C.S., and later Eleanor Roosevelt as Directors of the American Red Cross promoted and advocated for plasma collection (especially for the war in the South Pacific where whole blood in acid-citrate, the only available anticoagulant at the time, had a shelf-life in a refrigerator of two weeks which precluded an Ocean voyage). All units of fresh frozen plasma today (like COVID-19 Convalescent Plasma) are collected in CPD (Citrate-Phosphate-Dextrose) or CP2D having shelf-lives of ~ 1 year, and CCP is readily available by donation, effective in "high titer", and cheap to collect, process, and

distribute. 1 unit of FFP costs ~\$200 and can provide two CCP doses verse Regeneron's monoclonal cocktail which cost the U.S.A. taxpayers ~\$3000 – 15 times more expensive and COVID-19 has developed resistance since December 2021 rendering Regeneron's monoclonal cocktail of Casirivimab plus Imdevimab **USELESS.** As CCP is polyclonal and can be collected from individuals who have recently recovered from the latest mutation of COVID-19, CCP has the potential of always being somewhat effective.

So, Mr. President, why was PL-115-176 so threatening to the Medical-University-Pharmaceutical Industrial Complex? Well,...

1. Recruitment for Randomized Control Trials (RCT) would be impossible with the inability to investigate patients potentially for **placebo** groups. On August 12, 2020, when one of the named investigators of the FDA/Mayo Expanded Access (Compassionate Use) was asked this very question, the researcher's response was the following which is inconsistent with the Nuremburg Code, the Helsinki Accords, and the Belmont Report and should be denounced as coercion by every Intuitional Review Board (IRBs are all overseen by the FDA) in the United States of America:

Since April, the Trump administration has set aside **more than \$300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving high-risk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

- 2. Having been a VA Merit II Grant research recipient in the early 1990s in which the nominal award is the absolute total money received, the NIH Grants have funded medical researchers and the Universities are very cognizant that in the past the indirect moneys may almost double the awards. Is it so hard to reason why few researchers have questioned the NIH direction in the treatment of COVID-19? Application of PL-115-176 stifles all present and future RCTs by permitted every American the right of request for a Phase I-completed without having to participate in a RCTs.—BUT, PL-115-176 IS THE LAW OF THE LAND!
- 3. In November 2020, the local VA Infectious Diseases service of the St. Louis VAMC ordered the discontinuation of Remdesivir prescribed for my patients citing the VACO protocol in Attachment A. (This VA protocol has been completely wiped from the Internet subsequently probably by the VA.) The correspondence interaction between myself, the VA, Dr. Fauci's office, and the editors of *The New England Journal of Medicine* can be found in the attached data card in: 2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where we went wrong > 06 Appendices A-H > Appendix E—Correspondence with VA and NEJM Dec 2020.

- 4. On February 18, 2021, *The New England Journal of Medicine* published a three page editorial as an excuse for what subliminally had occurred for the previous 11 months regarding *Passive Immunization* in the FDA/NIH disorganized treatment of COVID-19. Louis Katz, M.D., former Chief Medical Officer at America's Blood Bank Center in Washington, was the sole author of this editoral: Katz LM: (A Little) Clarity on convalescent plasma for Covid-19. Initially published electronically on January 13, 2021, and republished as a hardcopy republished in the N Engl J Med, 2021 Feb 18; 384 (7): 666 668. https://www.nejm.org/doi/full/10.1056/NEJMe2035678. On March 2, 2021:
 - 783) NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health announcement is: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms

The actual clinic trial, *Convalescent Plasma in Outpatients with COVID-19 (SIREN C3PO)* NCT04355767, was:

https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1

There were no reported results on the NIH Clinical Trials website of which the NIH was making its decision to halt the trial. The trial was underpowered where there was no stratification by age, the exclusion criteria were arbitrary to an extreme, and the study was discontinued with recruitment of only half the number of planned patients. This study was run by: **SIREN**, **S**trategies to **I**nnovate eme**R**g**EN**cy Care Clinical Trials, https://clic-ctsa.org/node/9426.

The actual "results of this RCT" were finally published in hard-copy form on November 18, 2022. In my opinion, *this article is one of the most disingenuous research papers I have ever read*—and was unbecoming of *The New England Journal of Medicine*:

1014) 2021-11-18 Korley FK, Durkalski-Mauldin V, Yeatts SD, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswall S, Kaplan A, Lowell E, Mcdyer JF, Quinn J, Triulzi DJ, Van Huysen C, Stevenson VLM, Yadav K, Jones CW, Kea B, Burnett A, Reynolds JC, Greineder CF, Haas NL, Beiser DG, Silbergleit R, Barsa W, Callaway CW, for the SIREN-C3PO Investigators: Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO ClinicalTrials.gov number, NCT04355767.] https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true

The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. (Advarra is a propriety company which on their internet listing are: Industry Experts—The Advarra Advantage: Our Expertise:

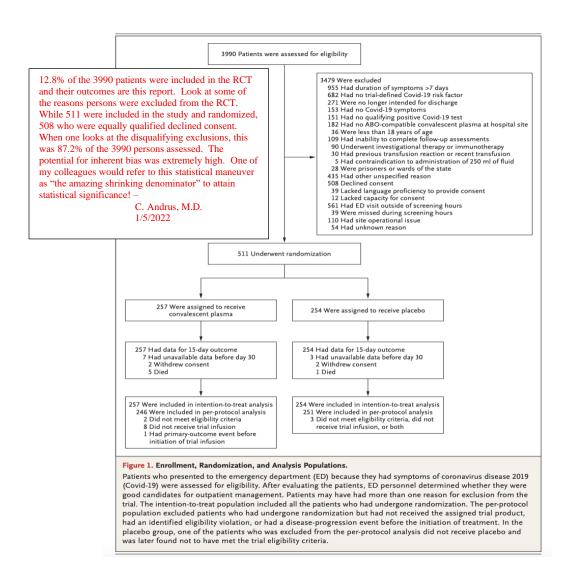
The Advarra advantage is built on our industry and domain expertise. Our experts are change agents and thought leaders with deep experience in clinical research. Together, we solve mission-critical challenges and bring life-changing therapies to participants faster. (Please note, Advarra's experts listed on their website https://www.advarra.com/about/industry-experts/ include NO MEDICAL CLINICIANS LIKE AN M.D. OR A D.O. In short, the SIREN-C3PO clinical trial NCT04355767 was reviewed by a proprietary company and NOT by any University School of Medicine IRB, any participating Hospital IRB, or the FDA's IRB directly.)

PLEASE note that the complete article and the supplementary appendix can be found:

Korley FK, Durkalski-Maudin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, et al., for the DIREN-C3PO Investigators*: Early convalescent plasma for high-risk outpatients with Covid-19. URL from article N Engl J Med 2021 Nov 18; 385: 1951-1960.

https://www.nejm.org/doi/10.1056/NEJMoa2103784 This reference from the article is just an abbreviation; The full article is

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true and the Supplementary Appendix which is very important can be found at (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf).



In Figure 1. **Enrollment, Randomization, and Analysis Populations**, of the 3990 patients presenting to the Emergency Room, 3479 (87.2%) were excluded as listed in the box above. The number of eligible patients that refused to participate in this placebo RCT was 508 and with the 561 that presented outside of ED screening hours and thus were rejected. These two exclusion factors totaled over twice as many patients (1069) as were included in this study of 511. What is more, when the NIH announced the closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum β that the researchers agreed upon for a valid study), it proceeded to conclude that early administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is most probably a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published.

It should also be noted that at the end of the author list on the front page of this article, it is stated: ...for the SIREN-C3PO Investigators* where the "**" refers to the statement in the right margin:

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org which is 20 pages long (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf) In this Supplementary Appendix major criteria for inclusion in the study changed from Protocol Version 1 of June 17, 2020 through Version 2 of July 2, 2020, Version 3 of September 7, 2020, Version 4 of November 3, 2020 to Version 5, February 16, 2021:

Has at least one study defined risk factor for severe COVID-19 illness:

Age \geq 50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression

Yet, in Table 1. Characteristics of the Patients at Baseline:

Characteristic	Convalescent Plasma	Placebo
	(N=257)	(N=254)
Median age (IQR)	54 (42-62)	54 (40-62)

there were patients of 42-49 years in the Convalescent Plasma group and patients of 40-49 years in the placebo group. Those patients should have been excluded due to their "youngness" that violated the stated inclusion criteria of all five Protocol versions of this trial. Were the SIREN-C3PO investigators, the NIH, and the editors of *The New England Journal of Medicine* being truthful to the American public? Has this paper done a disservice to the American public and to the World? As the NEJM attests to the participation in the *International Committee of Medical Journal Editors (ICMJE)*, they owe the American people an independent (independent from the U.S. Government and *The New England Journal of Medicine*) peer review of this paper with regards to appropriateness: Simply put, can this paper even conclude that which it concludes?

Mr. President, I apologize for the length of this cover letter trying to provide an overview summary of what is contained in my submission to you today. Besides suggesting that you have Drs. Fauci and Collins write monographs for you regarding the Pathophysiology of COVID-19 and therapies based on treating the pathophysiology, there are foundational flaws in our medical system that require addressing: failure of the IRBs; failure to implement PL-115-176, The Right to Try law; abridgement of American rights guaranteed by EMTALA; etc. to name but a few.

If I can provide clarification or suggestions in the future, please ask whatever you may of me as I am a physician and surgeon of the Veterans Health Administration, U.S. Department of Veterans Affairs. (This weekend our family drove to Atlanta as our second son (we have five boys) got married—now that our family is home, should you wish one of your people to contact me, please

call my wife Pam's cell phone: 314-809-9634 or our home phone: 314-455-9482. Thank you for taking this information under your consideration.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.

Former Professor of Surgery, Department of Surgery, Saint Louis University School of Medicine Physician and Surgeon and Chief of Unit II (SLU) General Surgery division, Surgical Service, St. Louis (John Cochran) VAMC

Home phone: 314-455-9482

Pam's cell: 314-809-9634

Cc:

Anthony S. Fauci, M.D.
Director of the U.S. NIAID
U.S. National Institutes of Health
U.S. Dept of Health & Human Services
5601 Fishers Lane, MSC. 9806
Bethesda, MD. 20892-9806
Re: Case # 12276

Phone: 301-496-5717 FAX: 301-402-3573

The Honorable Denis McDonough Secretary, U.S. Department of Veterans Affairs 810 Vermont Ave, NW Washington, DC. 20420 Denis.McDonough@va.gov

Catherine Mitrano, J.D. and Michael R. Hogan, J.D. Office of General Counsel (26)
Designated Agency Ethics Official (DAEO)
810 Vermont Ave, NW
Washington, D.C. 20420

Phone: 202-360-3598

closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum ß that the researchers agreed upon for a valid study), it proceeded to conclude that early administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is probably a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published.

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4.0 1 0.1 2022-09-11 Dear Mr. President Case Report EDIT 9-22-2022.pdf

150 Emerald Green Ct St. Louis, MO. 63141 September 11, 2022 (edited and completed 9/20-22/2022) (314) 455-9482 Pam's cell: 314-809-9634

President Joseph Biden
President of the United States of America
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500
202-456-1414

Re: NIH NIAID Case #12276 USPS Priority mail: 2022-09-11 Dear Mr. President Case Report cover letter

Dear Mr. President:

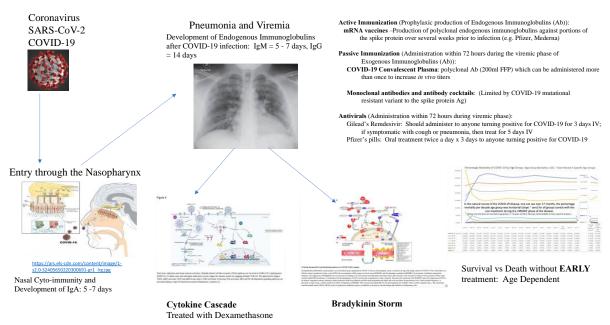
I apologize for the seemingly oppressive amount of material I present before you today. The case report that follows encapsulates our failings to individuals infected with coronavirus, SARS-CoV-2 (COVID-19) over the last 31 months.

Introduction:

As a federal physician and surgeon, it is my duty to the American people and to yourself as our nation's leader to state frankly that American Medicine failed the American people in the **treatment** of those infected with COVID-19. For the last 120 years when dealing with a novel infectious disease of which our immune system is naïve, American Medicine has always had one immediately available **treatment** of convalescent plasma from individuals that have previously recovered from the disease. Over the last two years with our continuing ongoing lack of understanding of how crucial past history should direct us, American Medicine **failed** to **treat** COVID-19 appropriately in a standardize fashion: **EARLY** (<72 hours) in the contraction of the disease (Figure 1):

- 1. Collate and incorporate in our knowledge-base as many elements as possible regarding the *Pathophysiology* of the coronavirus, SARS-CoV-2
- 2. Distinguish the **treatment** options of an infected individual vs prevention and prophylaxis of non-infected individuals based on the *Pathophysiology* of the coronavirus, SARS-CoV-2, COVID-19
- 3. Distinguish (1) **Early Treatment** (within 72 hours of symptomatology and diagnosis) during the **VIREMIC PHASE** of the coronavirus, SARS-CoV-2 from (2)**Late Supportive Therapies** during the overwhelming **Systemic Response Phases** of the *Cytokine Cascade* and the *Bradykinin Storm*.

Figure 1: Pathophysiology and Acute Treatment of COVID-19



1.002 2022-02-27 Pathophysiology and Acute Treatment of COVID-19

In dealing with any infectious disease one must (1) identify the source, (2) understand how it infects, (3) develop treatments for those that are infected, and (4) develop long-term methologies of protection and prevention for those who are <u>not</u> infected. In March 2020, American Medicine jumped over any organized treatment strategy in the individual patient infected with COVID-19 emphasizing instead future approaches of long-term protection and prevention while ignoring early available treatment methodologies for the COVID-19 infected individual patient. The case study that follows epitomizes where we are today 31 months after the beginning of the American epidemic. I emphasize *epidemic* as opposed to *pandemic* because throughout the last two+ years, the FDA, the NIH, and all of American Medicine have not been precise or completely accurate in our definitions, in our thought processes, and in setting appropriate goals. As the President of the United States, you are above all else the ethical, moral leader of this country which was unfortunately contradicted previously by a narcissistic, self-absorbed, unscrupulous mindset akin to the 7th grade playground bully encouraging a reign of terror / fear among all who participate in the schoolyard.

Case report:

A 66-year-old female patient last weekend who was visiting relatives in a contiguous state to her home developed a sore throat, headache, cough, coryza, and tested positive by a home nasal swab Ag-Ab test for COVID-19. She previously had received the two initial doses of the vaccine against COVID-19 and has had two boosters. The patient has a history of atrial fibrillation and is on Xarelto.

Knowing early administration of an antiviral or immunoglobin (within 5 days of symptomatology) will modify/diminish the symptoms of COVID-19, this well-educated patient immediately called her personal physician's office to request a script for the oral antiviral Paxlovid. She was informed that her long-time doctor would not prescribe any medications if she was in another state even though she was in a contiguous state. She went on-line to locate a pharmacy through the COVID-19 Test-to-Treat program where she could receive Paxlovid and was rejected. She went to a local Hospital Emergency room in that contiguous state where she was told she must be tested again. The patient related that the nasal swabbing was superficial, hurried, and inappropriately administered—and the resultant report of the hospital ER was Ag-Ab screening was negative. The ER doctor stated that even if this test was positive (and the athome test was absolutely positive and the patient was symptomatic), he would not give her a script for Paxlovid because he had never prescribed it before.

The patient went back on-line and found a proprietary teleconference physician service which deals with COVID-19, The patient paid the necessary fee (~\$140), and was assigned a physician who was two thousand miles away but who had a license in another contiguous state to the one she was at present within. Unlike all those previous healthcare personnel, this physician was not dismissive to the patient—he listened to the patient, reviewed her medication listing, and stated that Paxlovid was contraindicated as she was on Xarelto (rivaroxaban) placing her at a higher risk of hemorrhagic stroke with the combination of Paxlovid and Xarelto. He thus prescribed for her the present *Eli Lilly* monoclonal antibody bebtelovimab which is active against the omicron variant. The next day with the prescription in hand, the patient was infused with one intravenous dose of bebtelovimab in a small regional hospital of a second contiguous state. While the patient still had a significant sore throat and coryza 24 hours later, her overall systemic symptoms were minimal and 48 hours after the single infusion of bebtelovimab the patient felt much better. While the patient's severe cold-like symptoms of coryza, upper air way congestion, and cough are slowly improving, the patient had minimal systemic symptomatology, has no organ failure, and is alive.

Results:

Immunotherapy and antivirals should be administered within 5 days of symptomatology and diagnosis which is consistent with the pathophysiology of disease COVID-19 caused by coronavirus, SARS-CoV-2. (Appendix I)

The COVID-19 virion is an 80-120 nm RNA coronavirus which is mainly transmitted by a respiratory route. **Mr. President,** there is no such thing as an antiviral mask. N95 masks mean that 95% (a 0.95 confidence level) of particles below 300 nm will be obstructed affording a high-level (but not absolute) protection for the non-infected individual. For the infected individual in this case report, it is more important for this individual to where a mask. As the moist phlegm

particles in an infected individual from a sneeze or a cough are usually larger than 300 nm, masks are the best protection (not for the wearer) but for those being sneezed upon or coughed on by infected individuals. Thus, while wearing a mask provides the wearer theoretically ~95% obstructive protection from the coronavirus, SARS-CoV-2, that may be on the outside of such a mask, it is the embodiment of the Golden Rule for those infected with COVID-19 with regards to limiting exposure to the non-infected of humanity around them: *Do unto others as you would wish would do unto you.*

I. Ever since U.S. DHHS Secretary Azar on March 13, 2020, waived under his 1135 waiver authority of the Social Security Act retroactive to March 1, 2020, some aspects of the Emergency Medical Treatment and Labor Act (EMTALA) have been suspended. As few in the U.S.A. knew what this even meant, the guaranteed rights of every American under EMTALA of the COBRA of 1986 have been *de facto* abridged and suspended for the last 31 months to this very day. https://www.cms.gov/files/document/covid-19-emergency-declaration-waivers.pdf EMTALA (the Emergency Medical Treatment and Labor) Act of COBRA, Consolidated Omnibus Budget Act of 1986, PL-99-272) is the guarantee to all Americans when they present to hospital ERs of the following:

- 1. Resuscitation and stabilization,
- 2. Diagnosis and treatment, and
- 3. Disposition

If the Emergency Room physician had done what he did in a time when rights under EMTALA were intact and not waived initially by the Trump Administration (and continuing to this day by the Biden Administration), the physician and his hospital would each have faced \$50,000 fines adjudicated and levied by the U.S. Department of Health and Human Services (DHHS) on behalf of the patient. (**Mr. President,** please understand that the \$50,000 fines levied against the physician and the hospital are *NOT* covered by any malpractice carrier.) While the Trump Administration initiated the waivers, you renewed the waivers on February 24, 2021, and, as of August 18, 2022, CMS (Centers for Medicare and Medicaid Services) has sustained the waivers of EMTALA by stating that only when the COVID-19 Public Health Emergency (PHE) is officially concluded that the waivers involving **the abridgement of** individual American's rights under EMTALA will be terminated. (**Mr. President,** you have an obligation to the American people to conclude the present Public Health Emergency (**PHE**) --possibly by an Executive Order?!)

The Emergency Room physician epitomizes the confusion across the nation over the appropriate algorithm in the *EARLY treatment* (within less than 72 hours of diagnosis) of those infected with COVID-19. (Appendix I) Appendix II is a rough chronology of the mistakes from March 2, 2020 forward to the present, that both Administrations have been parties to. —while extremely lengthy, the rank-and-file American and the rank-and-file physician have little knowledge of "test and treat" and really don't know their options of antivirals and immunoglobulins within the first 72 hours of diagnosis. (Mr. President, this is rationing out of ignorance.)

II. While Dr. Adams had good intensions, on March 19, 2020, Jerome Adams, M.D., U.S. Surgeon General, published on the Internet a Public Service Announcement (PSA) that muddied the waters even more by stating that Americans who thought they were infected with COVID-19 should not go to a hospital emergency room so as not to contaminate others which is the continued pervasive mind-set even today.

Adams J: PSA, If You Are Sick. March 19, 2020.

https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/

As the Nation's doctor, I often get asked: What should I do if I think I might have coronavirus? Well, it is important to know the symptoms--they include: fever, cough, and shortness of breath. If you are having these symptoms or worry you might have coronavirus, please call your healthcare provider. We don't want you to go into the ER or the doctor's office without talking to them first because you might spread coronavirus to someone else. They will help you think through and learn how to react including figuring out where to go to get tested if necessary.

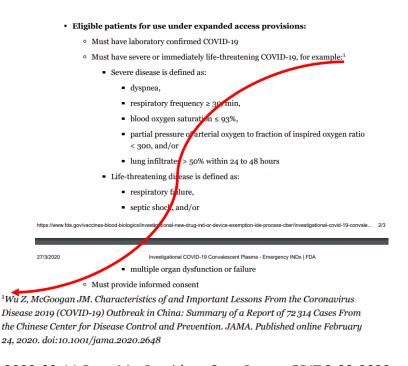
Dr. Jerome Adams, PSA, If You Are Sick, March 19, 2020.

III. On March 24, 2020, instead of recommending **EARLY ADMINISTRATION in the disease** (during the *viremic phase* ~72 – 96 hours after diagnosis) with COVID-19 Convalescent Plasma and the antiviral Remdesivir, the FDA recommended a **WRONG TREATMENT TIME** of the **LATE ADMINISTRATION in the disease** (during the *cytokine cascade* and *bradykinin storm* phases > ~72 hours after diagnosis). To this day, *de facto* **rationing**, is still present in the mindset of the majority of healthcare providers, the federal government, and the American people.

Figure 2:

2020-03-24 U.S. Food and Drug Administration: Investigational COVID-19 Convalescent Plasma – Emergency INDs, March 24, 2020.

https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf



Discussion:

Mr. President, while the physicians and administrators of the agencies (e.g.: FDA, CDC, NIH, BARDA, PHS, etc.) of the U.S. Department of Health and Human Services (DHHS) and the U.S. Department of Veterans Affairs will argue to discredit my submission to you, **Mr. President**, this Case Report is an anecdotal tale that **epitomizes** that which is occurring throughout the nation to COVID-19-infected individuals today:

(1) The Ag-Ab screening tests are reportedly ~82% - ~89% statistically sensitive. The calculation of "Sensitivity" —True Positive / (True Positive + False Negative) provides a "POSITIVE" for an Ag-Ab test which is statistically a "POSITIVE" for a medical screening test purposes and a repeat Ag-Ab screening test <u>DOES NOT NEGATE</u> the first result.

 $\frac{https://www.nottingham.ac.uk/nmp/sonet/rlos/ebp/sensitivity specificity/page four.html \#:\sim:text=Sensitivity y%20(the%20proportion%20of%20patients,true%20positive%20plus%20false%20negative.\&text=Specificity%20(the%20proportion%20of%20patients,true%20negative%20plus%20false%20positive. \label{eq:loss}$

Mr. President, there is no such thing as a "Best two out of three, or three out of five," with regards to the Medical Statistical Term: **Sensitivity**. Repeating the same medical "screening test" and choosing a possible "false" **negative result** as statistically better over a **positive** is an incorrect interpretation. That is why the accepted practice for medically statistics to reject the null hypothesis (H_o) (a true difference between to binary test groups) is a 0.95 confidence level which is roughly two Standard Deviations (SD) from the mean (actually, Z=1.96 at a CI=0.95).

https://www.westga.edu/academics/research/vrc/assets/docs/confidence_intervals_notes.pdf
While the Ag-Ab nasal swabs are the good for a rapid screen (RT-PCR is more sensitive), the Ag-Ab "COVID-19 screening tests" don't meet the absolute standard of a screening test. In short, if a screening test is positive within the first 72 hours, TREATMENT with an immunoglobulin(s) and/or an antiviral should be the STANDARD TREATMENT. (Using both immunoglobulin and antiviral are synergistic).

Mr. President, as Dr. Fauci and Dr. Collins are still U.S. Government employees, you might request their presence in *The Oval Office* to discuss with you an explanation as to why today in our national response to COVID-19 some Medical Tests (and Treatments) are accepted and others are rejected. The business community has used this ambiguity in their definitions and their applications of "products" to advantageously market products (and discredit the competition) throughout our society for years. Before your meeting with Drs. Fauci and Collins, you might wish to review Darrell Huff's Best Seller of the 1950s entitled: *How to Lie with Statistics* which can be accessed *in toto* in the Website below: https://online225.psych.wisc.edu/wp-content/uploads/225-Master/225-UnitPages/Unit-07/Huff StatisticsBook 1954.pdf A few unrelated examples from our time:

"four out of five dentists surveyed recommend sugarless gum for their patients who chew gum". https://knowyourmeme.com/memes/9-out-of-10-dentists p= 0.80

According to the little cartoon box for Cologuard television ads: "I'm convenient and find 92% of colon cancers...even in early stages. I'm for people 45 plus at

average risk for colon cancer, not high risk. p=0.92

https://www.youtube.com/watch?v=JsC3rmtzXP0

http://www.tarrantgidoctors.com/blog-

cologuard.html#:~:text=Cologuard's%20accuracy%20rate%20for%20detecting,14%25%20false%2Dpositive%20rate

COVID-19 RT-PCR versus Ag-AB test sensitivity "screening tests":

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2791915#:~:text=Antigen%20test%20sensitivity%20was%2050,CI%2C%2069%25%2D83%25:

Antigen test sensitivity was 50% (95% CI, 45%-55%) during the infectious period, **64%** (**95%** CI, **56%-70%**) compared with same-day RT-PCR, and 84% (95% CI, 75%-90%) compared with same-day cultures. Antigen test sensitivity peaked 4 days after illness onset at 77% (95% CI, 69%-83%).

November 5, 2021: Pfizer's novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in Interim Analysis of Phase 2/3 EPIC-HR study. P= 0.89% https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate

Pregnancy tests which have a whole range of sensitivities when the common misinterpretation is that the test answer should be binary: **Yes or No**: http://getthediagnosis.org/diagnosis/Pregnancy.htm

- (2) The patient with COVID-19 symptomatology of this **Case Report** presented within 5 days of COVID-19 positivity with the screening test which diagnosed COVID-19, and was rejected by her private doctor's office, the ER doctor, and the *Test and Treat* website.
- (3) Only when the individual newly-infected with COVID-19 finds a healthcare professional who is well-read and analytically discerning does the patient seem to have a chance.

Unlike Mrs. Biden and yourself when you immediately were initiated on Paxlovid, the individual patient in the community has to jump through many hoops due to physician, nurse practitioner, and public **ignorance**, **misinformation**, **and commercial upselling a product** (**or the competition having been negated**). The U.S. Department of Health and Human Services agencies, e.g.: FDA, NIH, CDC, PHS, BARDA, etc; U.S. Department of Veterans Affairs through the Veterans Health Administration; and all of American Medicine (e.g.: private and public practice; the Universities and Teaching Hospitals; Medical Publications like *The New England Journal of Medicine*, etc.) have **literally abandoned the individual American patient** when it comes to an organized treatment protocol universal for all those newly COVID-19 infected Americans. This is tantamount to *The Tuskegee Syphilis Experiment* (*TSE*) of the four middle decades of the twentieth century. When President Bill Clinton, who apologized for the U.S. Government a quarter-of-a-century later after the TSE had become public in 1972, there were only a few African-American sharecroppers of the study that were still alive.

So, **Mr. President**, when in the U.S.A., are we going to apologize to the families of the 1,000,000+ dead Americans from COVID-19 and those who survived compromised by organ failure, etc. in which **EARLY administrations of immunoglobulins and antivirals were** *NOT* **offered**, or just withheld due to healthcare worker ignorance, or administration denied within 5 days of identification of the disease in the individual even

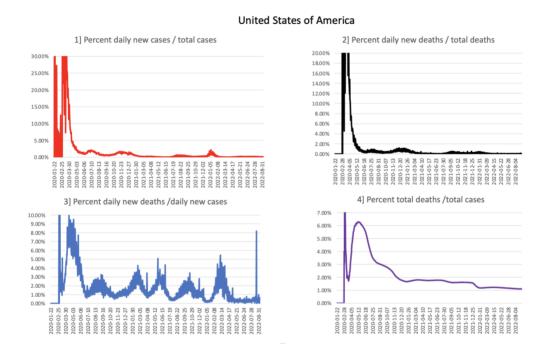
when the individual requested them? Refusal to give a drug or biologic that has completed a Phase I (Safety) Clinical Trial and a patient requests it off protocol is a violation of that patient's rights guaranteed by the Right to Tray Act of 2018, PL-115-176). The FDA and NIH have perpetuated this ambiguity by not declaring any "Phase I Clinical Trials *Completed*" even though *in practice* the FDA has deemed these drugs and biologics *de facto* safe prior to any distribution under any FDA EUAs. The U.S. Government has purchased millions of doses of vaccines, monoclonal antibodies, and antivirals for distribution but have NOT told the doctors or the patients how distribution is guaranteed to all. THIS is dysfunctional, irrational rationing emboldened by public and healthcare worker ignorance!

Mr. President, more than anything else for the people of the United States, you need to bring the COVID-19 epidemic officially "to closure" of the Public Health Emergency (PHE) by rescinding the COVID-19 National Emergency Declaration of March 13, 2020.—which will promote the legal termination of the EMTALA waivers as promised by the U.S. Department of Health and Human Services in August of this year.

The FDA, the NIH, and the VA have all been party to disinformation, which *de facto* obstructed the delivery of **EARLY TREATMENT** in the course of the COVID-19-infected individual's disease (< 72 hours from time of diagnosis). Unfortunately, disinformation, self-promotion, and withholding of treatments in the first few months (3/2020-11/2020) of the U.S. COVID-19 Epidemic, have pervasively advanced **that which Elisabeth Kubler-Ross** described in her landmark publication *On Death and Dying*: **Denial and Isolation, Anger, Bargaining, and Depression.** Only if the present animosity, intolerance, and hatred of your fellow man throughout the United States is discontinued, will we as a nation survive and be able to go forth successfully. We need to profess in our daily lives that which is on the inner north wall of the Lincoln Memorial:

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan—to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

Mr. President, we as a country need to forgive ourselves. Over the course of the last 30 years, we have become an extremely self-centered, financially-driven, intolerant society of the individual towards the individual with a differing viewpoint from ourselves. This has been magnified in our 31 month confrontation with the coronavirus, SARS-CoV-2, COVID-19 having become a seemingly insurmountable enemy. As with all novel infectious diseases in which humanity is initially immunologically naïve, the American epidemic began with a series of epidemic peaks **that went untreated in any EARLY organized fashion:** not with immunoglobulins nor antivirals. (Figure 3):



While there will be recurrent peaks in the future, over the course of time, the incidence of COVID-19 will taper asymptotically towards a low level as it becomes an ENDEMIC disease throughout our nation and the world. As the endemic development of any disease requires centuries to diminish, the transition to resolve as an Endemic Virus if **untreated** in the EARLY course of the infection (< 72 hours from diagnosis) in every individual, will be prolonged.

From March 2, 2020, to the present, we have officially **NOT TREATED in any EARLY organized fashion COVID-19** with immunoglobulins nor antivirals. My submissions to date have been to point out that we have not uniformly treated those infected with the COVID-19 disease in any organized fashion.:

Active immunization (vaccines) does not treat the disease in an infected individual—but, rather, stimulates the endogenous formation of B-cells (plasma cells) thus leading to the systemic IgM and IgG production in vaccinated individuals for prevention and prophylaxis.

Passive immunization (polyclonal exogenous antibodies—COVID-19 Convalescent Plasma—and monoclonal antibodies and monoclonal cocktails) and antivirals administered if given EARLY (within <72 hours diagnosis) are effective in the treating of the disease. This last month when Mrs. Biden and yourself were treated with Paxlovid, the antiviral was used to suppress and degrade the RNA of the active virus in your nasopharynx. While you both were previously stimulated systemically by an mRNA vaccine for your B-cells to produce monoclonal (or limited polyclonal) IgM and IgG systemically, your upper airways were naïve with regards to IgA production and thus unprotected when coronavirus, SARS-CoV-2 was detected on a nasal swab. In the future, anticipated nasal COVID-19 vaccines may address the lack of IgA in the

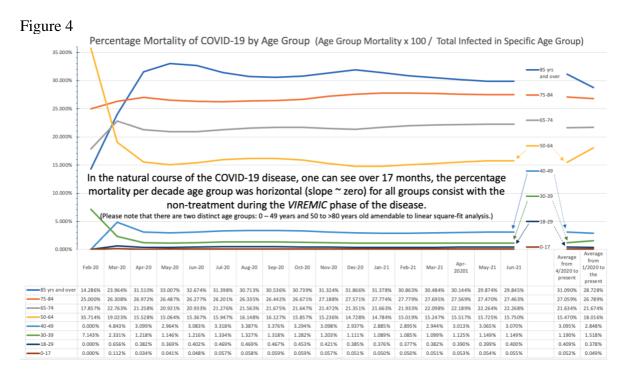
nares (the endogenous immunoglobulin in the nasal and upper airway mucosa) in individuals previously vaccinated and boosted with systemic vaccine antigens.

For the systemically unvaccinated (individuals who are completely naïve to coronavirus, SARS-CoV-2, COVID-19 have not developed systemic endogenous IgM and IgG), the severity of COVID-19 illness and mortality is greatest. As <u>no organized effort</u> in 2020 in the United States was initiated to treat **EARLY** (within < 72 hours of diagnosis) with immunoglobulins and antivirals, the mortality rates by age were static for months (See figure 3) and defined mathematically by:

Figure 4: Mortality linearly related in unvaccinated individuals

(x = age year; y = calculated mortality rate prevalence by age-year):

i. 0-45 years of age: y = 0.0008x - 0.0103 $R^2 = 0.825$ ii. 46 to >85 years of age: y = 0.0049x - 0.1216 $R^2 = 0.997$



In October 2020, the privileged unvaccinated individuals of Rudy Giuliani, Chris Christy, Ben Carson, M.D., and President Donald Trump contracted COVID-19. Immediately, within **72 hours of diagnosis**, all four were treated with a monoclonal antibody or cocktail and the antiviral Remdesivir (a 5 day course) and all survived. Reportedly, President Trump received Regeneron's monoclonal antibody cocktail within ~4 hours of diagnosis and a multiple day course of Remdesivir (I.V. bid) was initiated within 18 hours. In fact, after this treatment, President Trump bragged that he was cured! https://www.forbes.com/sites/roberthart/2020/10/08/while-trump-touts-cure-made-by-regeneron-its-ceo-is-a-member-of-trump-golf-club/?sh=6247615360c8

The combination of the administration of exogenous immunoglobulins and an antiviral are synergistic and should be **given within the first 72 hours after diagnosis** and **should be the Medical Standard of Care in the United States today for every man, woman, and child who contracts COVID-19** regardless of vaccination status or concomitant illnesses (e.g.: hypertension, diabetes, obesity, history of smoking, etc.)

In October 2020, the physicians caring for President Trump at Walter Reed Military Medical Center, FDA and NIH experts, medical publications, news commentators, the media, and the general public had the general impression that this combination was strictly experimental and thus not for the rank-and-file American. **WHAT A BUNCH OF HOGWASH!**Mr. President, this is the crux of the problem and the FDA, the NIH, the PHS, the CDC, Academic Medicine, all of United States Medicine, and all of the Federal Government were complicit in promoting this <u>HOGWASH</u>. As the case report of this summary exemplifies, AMERICAN MEDICINE failed the American people.

Mr. President:

- 1.) This occurred because from March 13, 2020, to the present, the United States has been in an official Public Health Emergency (PHE). On that day, Secretary Azar suspended parts of EMTALA retroactive to March 1, 2020, thus officially abridging some of every American's rights guaranteed by EMTALA:
 - a. Stabilization
 - b. Diagnosis
 - c. Treatment / Appropriate Disposition
- 2.) Your administration has continued the waivers on February 24, 2021; and, in August of 2022, CMS stated that the waivers would terminate once the Public Health Emergency (PHE) was declared concluded. **BUT, at present, there is no end in sight as the PHE has not been officially concluded** by you.
- 3.) In 2018, The Right to Tray Act became a Federal Law, PL-115-176, which stated that as soon an experimental drug or biologic had completed a Phase I (Safety) Clinical Trial, any American could request *off protocol* the experimental drug or biologic for the specific disease. The NIH and the FDA have facilitated that no drug (except Remdesivir) or biologic (the original Pfizer vaccine) as they are prescription drugs can be requested because all other Immunoglobulins and Antivirals to treat COVID-19 and the Vaccines to prevent and provide prophylaxis against COVID-19 retain their "Experimental status" under the EUAs. In short, the FDA has not officially declared all other drugs in the treatment of COVID-19 "SAFE" thus flagrantly avoiding application of the Right to Try act of 2018 (PL-115-176) by not officially declaring the Phase I Clinical Trials "ever being completed." Mr. President, how can the U.S. Government provide Oral Antivirals: Pfizer's Paxlovid and Merck's Lagevrio through the Test and Treat

Initiative https://aspr.hhs.gov/TestToTreat/Pages/default.aspx under EUA's if the FDA has not yet declared them *de facto* SAFE by the completion of Phase I clinical trials? https://www.cdc.gov/mmwr/volumes/71/wr/mm7125e1.htm . Mr. President, an opinion of Attorney General Garland regarding this conundrum might be helpful.

- 4.) Why would the NIH and FDA continue such misinformation? Randomized Controlled Trials (RCTs) usually compare the drug or biologic to a Placebo Control Group even though that may be Unethical. The use of placebos when the is a plethora of casematched controls during an epidemic especially with a disease of highly-variable, agecorrelated mortality IS HIGHLY QUESTIONABLE. Yet, the NIH, the VA, and BARDA funding always has the inherent risk of conflicts of interest. All Medical Research Clinical Trials since 2018 will have difficulty recruiting as on a drug or biologic is "SAFE" (Phase I Clinical Trials officially completed) the every patient with a disease has the right to go off protocol and ask for the drug or biologic through The Right to Try Act of 2018, (PL-115-176). All federal agencies to date have circumvented *The Right to Try Act of 2018*, (PL-115-176), ARE IN VIOLATION OF FEDERAL LAW, and have done an extreme disservice to the American people. Mr. President, you might suggest to Congress that they should inquire if PL-115-176 has ever been followed?
- 5.) Changing, misdirecting, or destroying URLs in Federal Government websites has been pervasive in the handling of U.S. Digital Documentation over the last twenty-five years, at least. *Electronic overwriting* of digital Federal documents without noting what has been overwritten is today *status quo*. In short, these practices allow for Destruction of Federal Government policies, documents, memos, handbooks, etc. **Digital destruction of (or legally concealing) Federal Documentation IS ILLEGAL; and yet, it is common daily practice in all the U.S. Departments and Agencies of the Executive Branch of the Federal Government of which you, Mr. President, are Constitutionally "The Boss."**

Mr. President, I initiated this cover letter and reiterate that: As a federal physician and surgeon, it is my duty to the American people and to yourself as our nation's leader to state frankly that American Medicine failed the American people in the **treatment** of those infected with COVID-19." It is my hope that you will take all of this under your advisement. Please note that much of my submission has previously been sent to the U.S. Copyright Office for preservation for history and the total submission today is for *educational purposes only*. I waive any personal financial rights to the material in this submission. Thus, the U.S. Government can copy, duplicate, and dispense anything in this submission, as I waive any personal protections regarding this submission.

I will also forward copies of this material to:

- 1. The Office of VA General Counsel as they are the: "Designated Agency Ethics Official" (DAEO) as they are the "safe harbor" regarding any submission of a VA employee to the Federal Government;
- 2. DVA Secretary McDonough, U.S. Department of Veterans Affairs;
- 0.1 2022-09-11 Dear Mr. President Case Report EDIT 9-22-2022

- 3. Anthony S. Fauci, M.D., Director of the NIAID;
- 4. Kara Harris, MPH, Section Chief for Controlled Correspondence and Public Inquires, Legislative Affairs and Correspondence Management, U.S. National Institutes of Health, and U.S. Department of Health & Human Services who when given my correspondence of June 2020 by Dr. Fauci responded by establishing: **NIH NIAID Case #12276.** Under the Freedom of Information Act, all in **Case file# 12276** is discoverable if requested formally by any and every American.
- 5. Abigail Carlson, M.D., formerly in the Division of Infectious Diseases, St. Louis VAMC, who I worked with as a colleague and a friend. Dr. Carlson now is in the Infectious Diseases Division of the CDC and can validate my sincerity and truthfulness in this submission to Dr. Walensky, Director of the CDC.

Mr. President, thank you for taking this information under consideration.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S. Physician and Surgeon, Surgical Services (112-jc), St. Louis VAMC, Veterans Health Administration, U.S. Department of Veterans Affairs

Cc:

Catherine Mitrano, J.D., and Michael R. Hogan, J.D. Office of General Counsel (26)
Designated Agency Ethics Official (DAEO)
810 Vermont Ave, N.W.
Washington, D.C. 20420

Phone: 202-360-2598

Re: NIH NIAID Case #12276 USPS Priority mail

Anthony S. Fauci, M.D.
Director of the U.S. National Institute of Allergy and Infectious Diseases
U.S. National Institutes of Health
U.S. Department of Health & Human Services

5601 Fishers Lane, MSC. 9806 Bethesda, MD 20892-9806

Phone: 301-496-5717 (last varified July 2020) FAX: 301-402-3573 (last varified July 2020)

Re: NIH NIAID Case #12276 USPS Priority mail

The Honorable Denis McDonough Secretary, U.S. Department of Veterans Affairs 810 Vermont Ave, NW Washington, D.C. 20420 Denis.McDough@va.gov

Re: NIH NIAID Case #12276 USPS Priority mail

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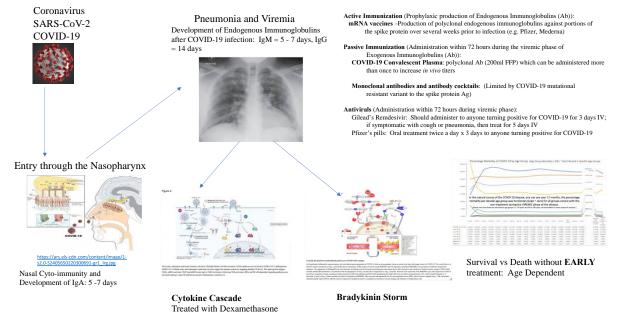
Re: NIH NIAID Case #12276 USPS Priority mail

Kara Harris, MPH
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Re: NIH NIAID Case #12276 USPS Priority mail

Appendix I: Pathophysiology, Clinical Identification, Treatment, Support, and Prevention



1.002 2022-02-27 Pathophysiology and Acute Treatment of COVID-19

- 2. Pathophysiology of the Coronavirus SARS-CoV-2 (COVID-19)
 - a. Size 80 -120 nm
 - b. Type: RNA coronavirus
 - c. Transmission: mainly respiratory (through the nares and oral inhalation) and possibly by contact of contaminated secretions
 - d. Entry through upper airway and through the attachment to the pneumonocytes of the lungs via the ACE2 receptors of the renin-angiotension-system (RAS)
 - e. Clinical expression:
 - i. Early (72 120 hours)—The Viremic Phase: Bilateral pneumonia, headaches, cough, malaise, diminished olfactory sensitivity etc.
 - ii. Late (> ~120 hours) host immunologic response, multisystem involvement including respiratory deterioration, etc.
 - 1. Cytokine cascade
 - 2. Bradykinin storm
 - f. Outcome: Mortality linearly related in unvaccinated individuals $(x = age\ year;\ y = calculated\ mortality\ rate\ prevalence\ by\ age-year)$:

i. 0-45 years of age: y = 0.0008x - 0.0103 $R^2 = 0.825$ ii. 46 to >85 years of age: y = 0.0049x - 0.1216 $R^2 = 0.997$

3. Clinical Identification:

- a. Polymerase Chain Reaction (PCR) https://www.ncbi.nlm.nih.gov/probe/docs/techpcr/ and https://pubmed.ncbi.nlm.nih.gov/21400274/
- b. Enzyme Linked Immunosorbent Assay https://www.ncbi.nlm.nih.gov/books/NBK555922/

4. Isolation, quarantine, masks, etc. (Please note, Mr. President, there is no such thing as an antiviral mask. N95 masks prevent passage of 95% (a 0.95 confidence level—2 standard deviations from the mean) of particles < 300 nm—thus 5% of COVID-19 particles (80 – 120 nm) can potentially get through by Brownian movement. This is somewhat analogous to a sparrow lighting in a cyclone fence and then flying through. All masks with regards to COVID-19 particles really more-protective to the individuals who come in contact with COVID-19 nares-positive individuals who are wearing masks. In this COVID-19 epidemic, the utilization of Masks epitomized one of the most noble of human attributes to which we aspire: *Do unto others as you would wish them to do unto you*.)

5. Therapies:

- a. Immunotherapies (Passive Immunization—Exogenous Antibodies) (optimum administration within 72-120 hours from diagnosis):
 - i. Polyclonal antibodies: COVID-19 Convalescent Plasma and Sera (These could be available as units or ½ units of convalescent fresh frozen plasma through every blood bank collection service throughout America including the non-for-profit American Red Cross and propriety blood banks like ImpactLife.
 - ii. Monoclonal antibodies and antibody cocktails.(Discussion of development of COVID-19 resistence by Molecular Darwinism):
 - 1. Eli Lilly's Bamlanivimab plus Etesevimab
 - 2. Regeneron's Casirivimab plus Imdevimab
 - 3. GlaxoSmithKline's Sotrovimab
 - 4. Eli Lilly's Bebtelovimab
- b. Anti-viral agents. (optimum administration within 72-120 hours from diagnosis)
 - i. IV agents, e.g.: Gilead's VEKLURY: Remdesivir, NDA#214787
 - ii. Oral agents, e.g.: Pfizer's Paxlovid and Merck Sharp & Dome's LAGEVRIO: molnupiravir
- c. Steroids -- Dexamethasone
- d. Other
- 6. Prevention:
 - a. Vaccines (Active Immunization—Endogenous Antibodies)
 - i. mRNA vaccines: endogenous development of IgM and IgG
 - ii. Nasal vaccines: development of IgA
 - b. Treatment with Passive Immunization Exogenous Antibodies
 - i. Exposed patients immediate dosing
 - ii. Immunosuppressed patients when weak or no response to mRNA vaccines
 repeated dosing every 8 weeks of Passive Immunization with repeat dosing intervals dosing with antivirals

- iii. Monoclonal gammopathies (monoclonal plasma cell tumors) e.g.: multiple myeloma as General Colin Powell had repeated dosing every 8 weeks of Passive Immunization with repeat dosing interval with antivirals
- iv. Prophylaxis with Passive Immunization in patients with other high risk situations as a bridge until Active Immunization has been acquired
- 7. Supportive Care:
 - a. O₂: Nasal prongs masks ventilators
 - b. Supportive medications: pressors, etc.
- 8. Outcomes:
 - a. Epidemiology:
 - i. Pandemic v Epidemic v Endemic
 - ii. Herd Immunity, what is it?
 - 1. By host disease acquisition
 - 2. By active immunization
 - 3. By passive immunization
 - b. Chronic Outcomes
 - i. Resolution without residuals
 - ii. Long-term COVID-19
 - iii. Chronic morbidities
 - iv. resultant organ failures
 - v. Deaths

Appendix II: An abbreviated timeline of Immunoglobulin and Antiviral Therapy:

I. In *The White House* on March 2, 2020, with several physicians present including Dr. Birx, Dr. Fauci, Dr. Hahn, Dr. Schleifer, etc., the President and Vice-President of the United States were introduced to the CEOs and Medical Directors of Pharmaceutical Drug and Biologics companies regarding anticipated future production of vaccines, monoclonal antibodies, and antivirals (Table 1). https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus Representatives of the Association of American Blood Banks (AABB) and the American Red Cross were not present. Unfortunately, Leonard Schleifer, M.D., PhD, CEO and Co-founder of Regeneron pharmaceuticals, explained monoclonal antibodies with a misnomer: Passive Vaccination which preclude the distinction between Active Immunization (vaccination to develop endogenous immunity—systemic IgM and IgG) and **Passive** Immunization (Immunoglobulins that are given as exogenous immunoglobulins— IgG: COVID-19 Convalescent Plasma [polyclonal antibodies] which were available and could be produced in mass quantities by the American Blood Banks as fresh frozen convalescent plasma (FFCP) and monoclonal antibodies and cocktails which were unavailable in March 2020, https://www.youtube.com/watch?v=31i6p stzW8 All the physicians in the room on that day failed the American people for NOT correcting Dr. Schleifer's misnomer of *Passive Immunization* as "Passive Vaccination." In strict medical terminology, Passive Vaccination DOES NOT EXIST. Which has helped facilitate the people of the United States of America down the wrong rabbit hole. (All these physicians were instructed regarding Active and Passive Immunization in some form of Immunology 101 in Medical School.)

On March 2, 2020, President Trump should have been advised: (1) that polyclonal antibodies were available in the form of COVID-19 Convalescent Plasma as soon as infected patients had convalesced (~4 weeks), (2) that a National COVID-19 Convalescent *Plasma Drive* directed and administered by the American Red Cross or other blood banking entity should have been initiated, and (3) an Organized, Federally-directed EARLY (within 72 hours of diagnosis of COVID-19 in an infected individual) administrative TREATMENT should have been afforded EVERY COVID-19 INFECTED MAN, WOMAN, and CHILD in the United States of America.

Table 1: Physicians present in *The White House* Conference on March 2, 2020 https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus Robert Redfield, M.D., Director, CDC Anne Schuchat, M.D., Principal Deputy Director, CDC Deborah L. Birx, M.D., Coordinator, *The White House*, Coronavirus response

Anthony S. Fauci, M.D., Director, NIAID

Stephen Hahn, M.D., FDA Commissioner

Leonard Schleifer, M.D., Ph.D., CEO and co-founder of Regeneron Pharmaceuticals

Paul Stoffels, M.D., Chief Science Officer, Johnson & Johnson

Mikael Dolsten, M.D., Ph.D., CEO, Novavax

II. On March 13, 2020, President Trump proclaimed a national emergency concerning the novel coronavirus disease (COVID-19) outbreak. $\underline{https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-national-emergency-proclamation-declaring-nation-declarin$ concerning-novel-coronavirus-disease-covid-19-outbreak/ Subsequent to this Proclamation of the same day and retroactive to March 1, 2020, U.S. Department of Health and Human Services Secretary Alex Azar issued a waiver or modification of requirements under Section 1135 of the Social Security Act which I allege became the de facto justification of abridgement of individual Americans' rights to ask for Passive Immunization and the antiviral drug Remdesivir guaranteed under EMTALA (the Emergency Medical Treatment and Labor Act of COBRA, Consolidated Omnibus Budget Act of 1986, PL-99-272), and the Right to Tray Act of 2018, PL-115-176. http://www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx Mr. President, it is my impression that your administration renewed the COVID-19 Emergency Declaration Blanket Waiver for Health Care Providers (COVID-19 EDBWHCP) thus continuing the de facto EMTALA suspension on February 19, 2021. The above related story seems to corroborate my impression in practice as of last weekend. https://web.archive.org/web/20210225112542/https://www.cms.gov/files/document/covid-19emergency-declaration-waivers.pdf The latest version of the **overwritten** of *COVID-19*

https://web.archive.org/web/20210225112542/https://www.cms.gov/files/document/covid-19-emergency-declaration-waivers.pdf The latest version of the **overwritten** of *COVID-19 EDBWHCP* states that these waivers will terminate at the end of the COVID-19 public health emergency (PHE). https://www.cms.gov/files/document/covid-19-emergency-declaration-waivers.pdf Well, Mr. President, when will the end of the COVID-19 public health emergency (PHE) be declared? Until the waivers of EMTALA are terminated, no American is guaranteed when they go to an ER that will be afforded their rights:

- i. To be stabilized on arrival to the ER
- ii. To be diagnosed
- iii. Appropriate disposition be afforded each and every patient, e.g.: treated appropriately and discharged appropriately after complete stabilization
- III. On March 19, 2020, Surgeon General Jerome Adams, M.D. in a PSA from *The White House* admonished all American the following:

 As the Nation's doctor, I often get asked: What should I do if I think I might have coronavirus? Well, it is important to know the symptoms--they include: fever, cough, and shortness of breath. If you are having these symptoms or worry you might have coronavirus, please call your healthcare provider.

 We don't want you to go into the ER or the doctor's office without talking to them first because you might spread coronavirus to someone else. They will help you think through and learn how to react including figuring out where to go to get tested if necessary.

 https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/
- IV. On March 19, 2020, Global Health NOW of Johns Hopkins Bloomberg School of Public Health ran an article: COVID-19's stop-gap solution until vaccines and antivirals are ready in which China had offered Italy 90 tons of COVID-19 Convalescent Plasma (~203,000 FFP units of COVID-19 Convalescent Plasma) https://www.globalhealthnow.org/2020-03/covid-19s-stop-gap-solution-until-vaccines-and-antivirals-are-ready

How can plasma be useful against the novel coronavirus?

When you recover from many viral diseases, you have in your blood what are called neutralizing antibodies. These are antibodies that kill the virus. Once you recover, the plasma be taken from donors. It's very safe. It's the same thing as using a blood donation except they don't take the red blood cells, they take the liquid. They take the plasma. It is itself a drug...it can be used for prevention of infection for people who are being exposed or it could be used for therapy for those who are sick.

It's not a vaccine. Think about it as the administration of a protein, it's a liquid that is given to people that gives them immunity.

Right. Because the vaccine would provoke the recipient's antibodies. You'll have the antibodies, but they won't be your antibodies—though it'll do the same thing. Right.

And if somebody is already sick, can the plasma help them?

Yes, it can be used for prevention or a treatment.

This strategy is already being used in China? Yes, in fact, the Chinese sent 90 tons of plasma to Italy.

V. On March 24, 2020, the FDA issued the following directive: Investigational COVID-19 Convalescent Plasma – Emergency INDs, March 24, 2020. https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf The FDA proposed inclusion criteria *incorrectly* directed / mandated administration of COVID-19 Convalescent Plasma only late in the disease (the cytokine cascade and the bradykinin storm) and not during the initial viremia of 72-120 hours after symptoms/diagnosis WHICH FOR 120 YEARS HAS BEEN THE CORRECT TIME TO ADMINISTER ANY FORM OF CONVALESCENT PLASMA OR SERUM. A completely unsubstantiated misinterpretation of a Chinese epidemiology article published in the *Journal of the American Medical Association* a month earlier was used by the FDA to justify this inclusion criteria. THE APPLICATION OF THIS MISINTERPRETATION IS COMPLETELY BOGUS, IS BEING

THIS MISINTERPRETATION IS COMPLETELY BOGUS, IS BEING APPLIED EVEN TODAY in community practice, AND THE FDA AND THE NIH KNOW THAT IT IS WRONG!

https://jamanetwork.com/journals/jama/fullarticle/2762130 The incorrect inclusion criteria is pervasive in practice even today has justified INCORRECT RATIONING of the antivirals and biologics. Officially, instead of the FDA and the NIH basing treatment on the Pathophysiology of COVID-19 and administering antivirals and biologics with 72 – 120 hours (the initial viremic period) from March 24, 2020 to August 28, 2020 and September 2, 2020, respectively wrong inclusion criteria was directed:

Eligible patients for use under expanded access provisions:

Must have laboratory confirmed COVID-19

Must have severe or immediately life-threatening COVID-19, for example:

Severe disease is defined as:

dyspnea,

respiratory frequency ≥ 30/min,

blood oxygen saturation $\leq 93\%$,

partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or

lung infiltrates > 50% within 24 to 48 hours Life-threatening disease is defined as: respiratory failure, septic shock, and/or multiple organ dysfunction or failure Must provide informed consent

Rear Admiral Denise Hinton, the FDA Chief Scientist, removed the Eligibility Criteria for Remdesivir on August 28, 2020 and for COVID-19 Convalescent Plasma on September 2, 2020.

- VI. On April 4, 2020, was the first day of the FDA/Mayo Clinic COVID-19 Expanded Access Program administered by Michael Joyner, M.D. digitally preserved by the Internet Archive (Wayback Machine). (The official FDA definition of Expanded Access is that all COVID-19 Convalescent Plasma (CCP) was administered under Compassionate Use which means the >94,000 CCP units can't be used for Randomized Controlled Trials (RCT) by the definition of the NIH and FDA and per section IV above, the >94,000 units of CCP were given at the WRONG time!)

 https://web.archive.org/web/20200404010134/https://www.uscovidplasma.org/
- VII. On April 24, 2020, President Trump introduced the idea of intravenous disinfectants which overshadowed the conference and distracted the discussion in which Dr. Hahn mentioned Convalescent Plasma and other anti-viral therapies.

 https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-april-24
- VIII. On May 1, 2020, President Trump in the Oval Office accepted the first shipment of the antiviral Remdesivir from the CEO of Gilead Sciences.

Mr. O'Day, Gilead Sciences CEO: What I'd like to say is that, you know, on behalf of Gilead, to the President's point, we feel a tremendous responsibility. We're humbled by this being an important first step for patients, for hospitalized patients. We want to make sure nothing gets in the way of these patients getting the medicine. So we made a decision to donate about 1.5 million vials of remdesivir.

The administration of Remdesivir would be given at the wrong time – late in the disease in those individuals with severe disease--using the same incorrect FDA Inclusion Criteria for CCP from May 1, 2020 to August 28, 2020. FDA Chief Scientist Hinton from the Inclusion Criteria in the EUA of August 28, 2020, stated: "...FDA is reissuing the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease.

https://web.archive.org/web/20200829175858/https:/www.fda.gov/media/137564/download

On October 22, 2020, Remdesivir (Velkury) was designated by the FDA as a new prescription drug, NDA 214787.

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf In November 2020, the VA Pharmacy Benefits Management Services 10PAP, Medical Advisory Board, and VISN Pharmacist executive must not have read Rear Admiral

Hinton's EUA revision of August 28, 2020, and the Inclusion Criteria was based on the EUA of May 1, 2020:

Inclusion Criteria

The following must be fulfilled to meet criteria for remdesivir Hospitalized with **SEVERE** COVID-19 (room air oxygenation saturation <94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is invasive or non-invasive ventilation or ECMO)***

https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf This URL cannot be found today even with the Internet Archive which suggests that the VA removed the discoverability of this incorrect (WRONG) directive:

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making to standardize and improve the quality of patient care, and to promote costs-effective drug prescribing. In CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL SCONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS PAT COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exc	clusion Criteria
If the	answer to ANY item below is met, then the patient should NOT receive remdesivir Treated for COVID-19 as an outpatient AST or ALT > 5 times the upper limit of normal Hospitalized patients but NOT requiring supplemental oxygen* Concomitant use of hydroxychloroquine or chloroquine Current eGFR < 30 mL/min**
Inc	lusion Criteria
The fo	ollowing must be fulfilled in order to meet criteria for remdesivir Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
Su	pplemental Information
or wh	nmended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving o remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration rapy has not been given
	hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be icated on a case by case basis
recom espe local	ents with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not mended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risk cially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on lguidance. madeshir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with

Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P

corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19

Updated version may be found at PBM INTERnet or PBM INTRAnet

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IX. In the Summer of 2020, the FDA / Mayo Clinic Expanded Access Program (compassionate use only so no data can be used for Prospective Clinical Trials) issued two reports on the safety of COVID-19 Convalescent Plasma:

2020-05-14 Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompas AM, Wiggins CC, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Buskirk CMV, Winters JL, Stubbs JR, Paneth NS, Casadevall A: Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. MedRxiv – Preprint May 12, 2020. https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1.full.pdf Ref 464

And

2020-07-19 Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, Wiggins CC, Senefeld JW, Klompas AM, Hodge DO, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimabal RJ, Bauer PR, Blair JE, van Buskirk CM, Winters JL, Stubbs JR, van Helmond N, Butterfield BP, Sexton MA, Soto JCD, Paneth NS, Verdun NC, Marks P, Casadevall A, Fairweather D, Carter RE, Wright RS. COVID-19 Convalescent Plasma in 20,000 hospitalized patients. Mayo Clin Proc September 2020; 95(9): 1888-1897. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7368917/pdf/main.pdf (ref 521)

Although these studies were funded by multiple agencies of the Federal Government, were listed on https://clinicaltrials.gov/, and COVID-19 Convalescent Plasma was deemed SAFE by these two studies, that "SAFETINESS" in 20,000 people under the guise of "compassionate use only" **disqualified the literal conclusion of a Phase I trial** and thus the Right to Try Act of 2018, (PL-115-176) was circumvented by the FDA and the NIH.

I submitted my analysis on 2020-06-08 to Dr. Fauci's office:

Andrus CH: Time: The Crucial Independent Variable of the COVID-19 Pandemic, U.S. Copyright Office, Library of Congress, 2020-06-08, Txu002199029. <a href="https://web.archive.org/web/20210904014401/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=9&ti=1%2C9&Search_Arg=Andrus+Charles+H&Search_Code=NALL&CNT=25&PID=DvTGOW_Qvd_foYxTFrVcdewL3ktMCwz&SEQ=20210425193720&SID=1

Dr. Fauci turned over the material to Kara Harris to respond to me and in her response she established NIH NIAID Case #12276. (Ref 490 and also)

Possibly in response to my submission of June 8, 2020, eleven days later on the Friday afternoon of June 19, 2020, *The White House* Press Secretary, Ms. McEnany in the segment 42.55 minutes to 44.43 minutes of

https://www.youtube.com/watch?v=GxX6CgI7RJ4 discussed COVID-19 Convalescent Plasma. **Mr. President,** please note that Ms McEnany is a lawyer and during this part of the News Conference seemed very uncomfortable announcing:

...Finally, well second, to finally, we are encouraged that we continue to gather positive data on a number of therapeutics: heparin; dexamethasone or steroids as it's more commonly known; convalescent plasma; and Remdesivir have all shown promise in treating coronavirus. Preliminary findings in a large UK-based recovery trial found that when steroids were used there was a 30% reduction in death for coronavirus patients on ventilators. The FDA is reviewing this recovery trial data now. Additionally, on convalescent plasma there's more encouraging news in partnership with mayo clinic the Trump administration move very quickly on this therapy and it's earliest days recognizing that it showed promise. Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promising--this has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages. The lead investigator of this Mayo Clinic study, Dr. Michael Joyner, summed up his work in saying that convalescent plasma "continues to look promising" noting the "excellent news of this study which covered a diverse population of patients about 20% were African-American, nearly 35% Hispanic, 5% Asian, and 40% women. Prior experience with respiratory viruses and some data that have emerged globally suggest convalescent plasma has the potential to lessen the severity or shorten the length of the illness caused by COVID-19. The results from the Mayo underscore that promise. As you can see, the Trump administration and FDA led on identifying convalescent plasma as a therapeutic and the results are encouraging... (Ref 495)

On July 22, 2020, I submitted my next analysis: Andrus CH: The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma. U.S. Copyright Office, 2020-07-22, TXu002214049. <a href="https://web.archive.org/web/20210904020833/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=6&ti=1%2C6&Search_Arg=andrus+charles+h&Search_Code=NALL&CNT=25&PID=cXfFuGrmHQvLVILvfNNt7Yjwh73ImgQ&SEQ=20210512081428&SID=1

On July 30, 2020, Members of the COVID-19 *White House* Commission accompanied President Trump to the headquarters of the American Red Cross: President Trump visits the American Red Cross. To highlight need for convalescent plasma during COVID-19. (Ref 527) https://www.redcross.org/about-us/news-and-events/press-release/2020/red-cross-highlights-need-for-convalescent-plasma-during-covid-19.html

On the same day, FDA Commission Steven Hahn, M.D. released his PSA. (An appeal by the FDA Commissioner on the same day as the American Red Cross visit by President Trump soliciting patients recovering from COVID-19 to donate COVID-19 Convalescent Plasma.) https://www.youtube.com/watch?v=PIX15rWdBbY. (Ref 528) and Dr. Birx also suggests need for CCP: McKend E: Dr. Birx: Plasma donations needed as coronavirus cases spike nationwide.

https://spectrumnews1.com/ky/lexington/health/2020/07/30/dr--birx--plasma-donations-needed-as-coronavirus-cases-spike-nationwide (Ref 530)

In early August 2020, multiple studies RECOMMENDED THE ADMINISTRATION OF CCP **EARLY** in the course of the disease after President Trump's visit to the American Red Cross:

On August 4, 2020: Dockser Marcus A: Convalescent plasma reduced death rate among Covid-19 patients, study data signals—Hospitalized patients who got earlier transfusions of blood plasma rich in antibodies to the coronavirus show a lower mortality rate. Wall Street Journal.

https://www.wsj.com/articles/convalescent-plasma-reduced-death-rate-among-covid-19-patients-study-data-signals-11596594390 (Ref 536)

Hospitalized Covid-19 patients who received transfusions of blood plasma rich with antibodies from recovered patients reduced their mortality rate by about 50%, according to researchers running a large national study.

The researchers presented their data analysis Saturday in a webinar for physicians interested in learning about so-called convalescent plasma, with data slides that were reviewed by The Wall Street Journal. The researchers said they saw signs that the treatment might be working in patients who received high levels of antibodies in plasma early in the course of their illness. They based their conclusions on an analysis of about 3,000 patients.

Patients who at three days or less after diagnosis received plasma containing high levels of antibodies against the coronavirus had a mortality rate of 6.6% at seven days after the transfusion. That compared with a mortality rate of 13.3% for patients who got plasma with low levels of antibodies at four days or more after diagnosis. That indicates reduced mortality of about 50%, the researchers said.

At 30 days after transfusion, the mortality rate was reduced by about 36%, investigators reported

August 6, 2020: Hegerova L, Gooley TA, Sweerus KA, Maree C, Bailey M, Dunleavy V, Patel K, Alcom K, Haley R, Johnsen JM, Konkle BA, Lahti AC, Alexander ML, Goldman JD, Lipke A, Lim S, Pauk JS, Pagel JM: Use of convalescent plasma in hospitalized patients with COVID-19: case series. Blood 6 August 2020; 136 (6): 759-762. (ref 538)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414587/pdf/main.pdf

In conclusion, the current study suggests that CP use in severe and critically ill patients with COVID-19 may improve survival if given early in the course of disease. The efficacy as a potential therapy needs further study in well-designed trials to better understand the contribution of CP to outomes in COVID-19.

2020-08-06 Bloch EM: Convalescent plasma to treat COVID-19. Convalescent plasma to treat COVID-19. Blood 6 August 2020; 136 (6): 654-655. (Ref 539) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414591/pdf/main.pdf

In conclusion, observational studies and compassionate use programs have been instrumental in the mobilization of CCP to contend with a global health emergency. Although safety has been addressed, efficacy data are critically needed to transition CCP's status from an investigational product to a standard therapy. The latter has practical ramifications, offering a formal mechanism for reimbursement and thus durable treatment strategy. Broadly, COVID-19 presents a rare opportunity to study

CP. If shown to be effective, CP would offer a scalable model that could be applied both to the current pandemic as well as to future emerging infectious diseases. It could also facilitate development of hyperimmune globulin and vaccine design. Clinical trials are already under way to address the uncertainty of use. Nonetheless, harmonization of efforts is needed along with creative approaches to overcome looming obstacles, such as pairing of trials of similar design and/or metanalysis. We must not be left wondering whether the intervention worked after the pandemic wanes.

2020-08-06 Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, Li J, Wang Z, Wu W, Wu M, Li W, Li L, Cai Y, Bosco B, Zhong A, Liu X, Lv T, Gan Z, Chen G, Pan Y, Liu C, Zhang K, Xu X, Wang C, Wang Q: Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood 6 August 2020; 136 (6): 755-758. (Ref 540) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414593/pdf/main.pdf

Experience from SARS-CoV-1 shows that convalescent plasma is most effective when administered shortly after symptom onset, typically within 2 weeks.7,14,17 The study by Liu et al¹⁶ showed that the effect of CCP was similar in an interval of 3 weeks' duration of symptoms. We compared the time to clinical improvement in patients with different therapy timings in our cohort, including 1 to 4 weeks, 5 to 6 weeks, 7 weeks, and 8 weeks after symptom onset. The results showed that the median time to clinical improvement was ;10 days in the 1 to 4 weeks', 5 to 6 weeks', and 7 weeks' groups. However, the time to clinical improvement was significantly prolonged in the \$8 weeks' group (Figure 1I).

In summary, we analyzed a large cohort of patients with COVID19 who received CCP and provide detailed evidence regarding their clinical improvement. Although the homogeneous data obtained from a single center may reduce some biases, there could inevitably be some confounding factors (eg, biased patient assignments) in this retrospective study. In addition, complete data on neutralizing antibody titers in CCP units were not available, limiting the power of evaluating the correlation between the quality of donor plasma and efficacy. Moreover, a stratified analysis of cases of severe and critical patients could not be performed due to the low proportion of critical patients. This analysis differs from existing studies in that its dynamic laboratory observations using large-scale data make it possible to analyze the potential therapeutic mechanism of CCP, recognize the characteristics of responders and nonresponders, and identify the indications and timing of therapy.18 Our results suggest that CCP, transfused even after 2 weeks (median of 45 days in our cohort) of symptom onset, could improve the symptoms and mortality in patients with severe or critical cases of COVID-19. We anticipate that this study could shed new light in clinical practice and monoclonal antibody development for COVID-19.

2020-08-06. Tobian AA, Shaz BH: Earlier the better: convalescent plasma. Blood 6 August 2020; 136 (6): 652-653. (Ref 540) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414595/pdf/main.pdf

Convalescent plasma is one of the best therapies currently available to treat COVID-19. However, critical questions on timing of treatment in the disease course and dose (volume and antibody titer levels) need to be answered. These answers will also help prepare us for other passive antibody treatments (eg, hyperimmune globulin made from convalescent plasma and monoclonal antibodies). The medical community

must work together to battle this deadly disease in order to determine the best therapies and reduce mortality.

2020-08-07 U.S. Food & Drug Administration: Donate COVID-19 Plasma. (Ref 542) http://web.archive.org/web/20200816041956/https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma

Anticipating that better access to COVID-19 Convalescent Plasma (CCP) would be announced, a series of events that follow demonstrate how wrong CCP access was rolled out by the Trump Administration. In fact, the article references that follows should have been decried by every Institutional Review Board in the nation as what is implied is **Unethical Coercion**:

2020-08-12 Kozlov M: Two Washington U. doctors lead national effort to study new COVID-19 treatment. St. Louis Post-Dispatch Aug 12, 2020. (Ref 543) https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article_ccec0f56-4493-5a26-8601-45e35d364b2d.html

Since April, the Trump administration has set aside **more than \$300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving high-risk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

Also on August 12, 2020, the FDA/Mayo Clinic Expanded Access Program announced, if given EARLY, that even in their "Compassionate Use" project patient mortality was significantly down:

Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Soto JCD, Baker SE, Shepherd JRA, van Helmond N, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whenlan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather DL, Wright RS, Carter RE, Casadevall A: Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: Initial three-month experience. Version 1. medRxiv Preprint. 2020 Aug 12. (Ref 544) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7430623/?report=printable

Abstract ...Participants: Adult participants enrolled and transfused under the purview of the US Convalescent Plasma EAP program between April4 and July 4, 2020 who were hospitalized with (or at risk of) severe or life threatening acute COVID-19 respiratory syndrome. Intervention: Transfusion of at least one unit of human COVID-19 convalescent plasma using standard transfusion guidelines at any time during hospitalization. Convalescent plasma was donated by recently-recovered COVID-19 survivors, and the antibody levels in the units collected were unknown at the time of transfusion. Main Outcomes and Measures: Seven and thirty-day mortality. Results: the 35,322 transfused patients had heterogeneous demographic and clinical characteristics. This cohort included a high proportion of critically-ill patients, with 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion. The seven-day mortality rate was 8.7% [95% CI 8.3-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis (p <0.0001).

X. When President Trump announced COVID-19 Convalescent Plasma (CCP) at the Sunday afternoon, August 23, 2020, *White House* press conference President Trump anticipated a bump in the poles prior to the next day's start of the Republican National Convention. Academic / University researchers / physicians within 24 hours criticized the announcement. References 551 to 553 in 20 2022-05-30 annotated Bibliographic Timeline References present the initial FDA response. In fact, the FDA released Reference 554 confirmed what the researchers in early August 2020 had already stated.

FDA News Release: FDA issues emergency use authorization for Convalescent Plasma as potential promising COVID-19 treatment, another achievement in Administration's fight against pandemic. U.S. Food & Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency's ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum, this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.

Today's action follows the FDA's extensive review of the science and data generated over the past several months stemming from efforts to facilitate emergency access to convalescent plasma for patients as clinical trials to definitively demonstrate safety and efficacy remain ongoing.

The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19.

Alex Azar, Health and Human Services Secretary:

"The FDA's emergency authorization for convalescent plasma is a milestone achievement in President Trump's efforts to save lives from COVID-19," said Secretary Azar. "The Trump Administration recognized the potential of convalescent plasma early on. Months ago, the FDA, BARDA, and private partners began work on making this product available across the country while continuing to evaluate data through clinical trials. Our work on convalescent plasma has delivered broader access to the product than is available in any other country and reached more than 70,000 American patients so far. We are deeply grateful to Americans who have already donated and encourage individuals who have recovered from COVID-19 to consider donating convalescent plasma."

Stephen M. Hahn, M.D., FDA Commissioner:

"I am committed to releasing safe and potentially helpful treatments for COVID-19 as quickly as possible in order to save lives. We're encouraged by the early promising data that we've seen about convalescent plasma. The data from studies conducted this year shows that plasma from patients who've recovered from COVID-19 has the potential to help treat those who are suffering from the effects of getting this terrible virus," said Dr. Hahn. "At the same time, we will continue to work with researchers to continue randomized clinical trials to study the safety and effectiveness of convalescent plasma in treating patients infected with the novel coronavirus."

Scientific Evidence on Convalescent Plasma

Based on an evaluation of the <u>EUA criteria</u> and the totality of the available scientific evidence, the FDA's Center for Biologics Evaluation and Research determined that the statutory criteria for issuing an EUA criteria were met.

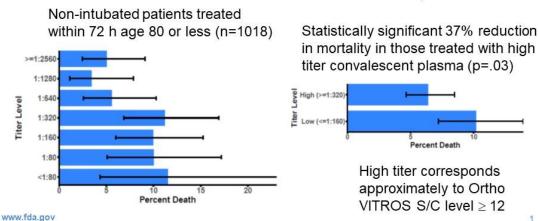
The FDA determined that it is reasonable to believe that COVID-19 convalescent plasma may be effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients. The agency also determined that the known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product and that that there are no adequate, approved, and available alternative treatments.

The EUA is not intended to replace randomized clinical trials and facilitating the enrollment of patients into any of the ongoing randomized clinical trials is critically important for the definitive demonstration of safety and efficacy of COVID-19 convalescent plasma. The FDA continues to recommend that the designs of ongoing randomized clinical trials of COVID-19 convalescent plasma and other therapeutic agents remain unaltered, as COVID-19 convalescent plasma does not yet represent a new standard of care based on the current available evidence.

The EUA remains in effect until the termination of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19. The EUA may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.

COVID-19 Convalescent Plasma Reduction in Death at 7 Days





The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products

While the previous FDA graphs demonstrated that higher titer COVID-19 Convalescent Plasma was significantly effective (p= 0.03) in reducing mortality, the FDA, the NIH, and *The White House* failed to delineate the significance of their graphic report. Mr. President, what is worse, from High School Chemistry, C₁ x V₁ = C₂ x V₂ corroborates that a doubling of the volume administered to the patient will double the concentration (titer of immunoglobulins) circulating in the patient's serum. For the last 25 months, the FDA has WRONGLY "emphasized" the Ultimate Importance of High Dose (HD) versus Low Dose (LD) COVID-19. In fact, one can double, triple, or quadruple the titer just by adding additional volumes of COVID-19 Convalescent Plasma.

Mr. President, <u>PLEASE</u> take it from this General Surgeon, the <u>only difference of</u> the same volume of fresh frozen plasma (FFP) administered for clotting factors during an operation versus from fresh frozen plasma of COVID-19 Convalescent Plasma (CCP) in the treatment of COVID-19 is that **CCP FFP** contains some concentration (titer) of Immunoglobulins specifically directed against antigens of Coronavirus, SARS-CoV-2.

Table 1: Conversion Low Dose COVID-19 Convalescent Plasma to High Dose COVID-19 Convalescent Plasma (CC-FFP) by increasing administration volume:

Titer of a Dose (200 ml) of CC-FFP	C1: Relative Polyclonal Antibody Units (RPAU)	V1: Std Volume of CC-FFP (200 ml = 1/2 unit of CC-FFP)	RPAU x 200 ml STD RPAU in STD VOL	C1 x V2= RPAU x 400 ml	C1 x V2= RPAU x 800 ml	C1 x V2= RPAU x 1600 ml
		std dose vol	RPAU x 200 ml= 1/2 unit of CC-FFP	RPAU x 400 ml = 1 unit of CC-FFP	RPAU x 800 ml = 2 units of CC-FFP	RPAU x 1600 ml = 4 units of CC-FFP
Very low titer <1:80 dilution	<80					
Low titer 1:80 dilution	80	200	16,000	32,000	64,000	128,000
Low titer 1:160 dilution	160	200	32,000	64,000	128,000	256,000
Low titer - 1:320 dilution	320	200	64,000	128,000	256,000	512,000
High titer 1:640 dilution	640	200	128,000	256,000	512,000	1,024,000
High titer 1:1280 dilution	1280	200	256,000	512,000	1,024,000	2,048,000
High titer ≥ 1:2560 dilution	2560	200	512,000	1,024,000	2,048,000	4,096,000

The shaded areas represent "High Dose administrations" or conversions to "High Dose administrations" of COVID-19 Convalescent Plasma by infusing a full unit of CC-FFP, doubling the units administered or quadrupling the units administered (e.g.: 1 unit, 2 units, 4 units) so as to exceed threshold of survivability at a range of 3%-5% when the Relative Polyclonal Antibody Units x volume equals or exceeds 128,000. Since September 2, 2020, the FDA, the NIH, etc. have touted to the American people that in fine print that: By the **EARLY** (<72 Hours from

diagnosis) **TREATMENT** of a newly acquired infection of coronavirus SARS-CoV-2 (COVID-19) with High Dose COVID-19 Convalescent Plasma (CCP) **ONLY**: "HIGH DOSE COVID-19 Convalescent Plasma is BETTER than LOW DOSE COVID-19 Convalescent Plasma" with **better survival**. Thus, from the FDA's graph above:

- (1) for (high dose) titers of 1:640 dilution to > 1:2560 dilution, **200 ml** (1/2 CC-FFP unit) IS MOST protective (more efficacious) titers (~3-5% death rate)
- (2) for an (intermediate dose) 1:320 dilution (~12% death rate), **400 ml** (1 CC-FFP unit) would be equivalent to the absolute neutralizing antibodies in 200 ml of a 1:640 dilution
- (3) for (low dose) titers of 1:160 and 1:80 dilutions (~10% death rate), **800 ml and 1600 ml, respectively** (2 CC-FFP units and 4 CC-FFP units, respectively) are adequate.

By increasing the administration volumes of Low Dose COVID-19 Convalescent Plasma or by concentrating (pooling multiple units) Low Dose COVID-19 Convalescent Plasma into COVID-19 Convalescent Serum, effective Passive Immunization with mortality rates of 4%-5% averaged across all age groups should have been accomplishable (from the FDA graph). Unfortunately, the FDA officially permitted administration of CC-FFP only in hospitalized patients; and the majority of the >772,000 CC-FFP doses all going to hospitalized patients were at the WRONG TIME--late in the disease--during the cytokine cascade and the bradykinin phases from at least April 2020 to the present. Can you imagine the decrease in mortality if the CC-FFP had been given HD AS AN IMMEDIATE, EARLY TREATMENT FOR NEWLY DIAGNOSED COVID-19 in all patients with COVID-19 as is implied by the FDA in the graph above !?!?!

In the letter: **1.0 2021-11-02 Dear Mr President Biden and ACS President Freischlag** within this present submission today, 9/22/2022:

½ unit of (Fresh Frozen Plasma) FFP (1 "dose") is ~200 ml; one unit of FFP is ~400 ml; and two units of FFP are ~800 ml. As a Vascular Surgeon, Dr. Freischlag-Julie, have you ever observed the unlikely fluid-overload of an adult patient strictly due to the tremendous volume of only 1 or 2 units (400 ml or 800 ml) of Fresh Frozen Plasma (FFP) administration? – I doubt it (Julie, please excuse my sarcasm as we surgeons have used FFP in blood component volume expansion when required throughout our professional lives with minimal complications.)!

In short, President Trump's politicization gambit of CCP <u>failed</u>.

Reference 558 explains why President Trump's announcement backfired. By discontinuing the Mayo Clinic / FDA Expanded Access program, there was no easy, official mechanism in place for patients to just ask for COVID-19 Convalescent Plasma because the FDA and NIH had been disregarding the implementation (and still are) of The Right to try Act of 2018 (PL-115-176):

Gallagher C: Expanded access program for convalescent plasma discontinues enrollment as FDA authorizes its emergency use. Mayo Clinic News Network, August 23, 2020. https://newsnetwork.mayoclinic.org/discussion/expanded-access-program-for-convalescent-plasma-discontinues-enrollment-as-fda-authorizes-its-emergency-use/

2020-08-23 Andrus CH: Re: Thousands of Americans are *needless dying* because the FDA is illegally ignoring PL 115-176 – The *Right to Try Law*^{1,2} and COVID-19 Convalescent Plasma has <u>NOT</u> been given as Prophylaxis and Early after COVID-19 positivity conversion. **Letter mailed to President Trump and the offices of the U.S. Senate.** [In the attached UHS-I Card: 06 Appendices A-H copy/01 Dear Members of Congress and President Trump 8_23_2020] I would also mailed 437 letters to the U.S. House of Representatives. While I did not received any responses, Rear Admiral Denise Hinton, R.N., M.S., FDA Chief Scientist removed the Severe Disease Inclusion Requirement for both COVID-19 Convalescent Plasma (CCP) and Remdesivir on September 2, 2020 and August 28, 2020, respectively.

(2020-08-28 Andrus CH: Re: This is a cover letter to the Congressional Staffer who will initially read the attached packet. After you read this cover letter, please bring it to your Chief of Staff so he or she might assess the importance of showing it to the Congressman or Congresswoman for whom you work. Letter to the Offices of the U.S. House of Representatives. [In the attached UHS-1 Card: 06 Appendices A-H copy/02 Dear Members of the US House of Representatives 8_28_2020])

2020-08-24 Thomas K, Fink S: F.D.A. 'Grossly misrepresented' blood plasma data, Scientists say. Many experts—including a scientist who worked on the Mayo Clinic study—were bewildered about where a key statistic came from. *The New York Times*

 $\underline{https://web.archive.org/web/20200825025014/https://www.nytimes.com/2020/08/24/health/fda-\underline{blood-plasma.html}}$

2020-08-24 Navarro P: Peter Navarro speaks with reports the day after the EUA announcement regarding COVID-19 Convalescent Plasma. https://www.c-span.org/video/?475057-101/peter-navarro-speaks-reporters

...kinds of successes he has last thing I want to do is talk a little bit about this cot convalescent plasma this is a great thing for the American people cob lesson plasma can reduce the mortality rate by 35 percent 35 percent and. If you see controversy in the news. You should think about this. There should absolutely be no controversy about convalescent plasma this is a therapy that's been used across many diseases for many decades the odds of it. Hurting you are close to 0 the odds of it helping you are close to 100 percent the only issue is how much it can help and according to the f.d.a. a 35 percent reduction in mortality so for me this convalescent plasma debate is in some sense a litmus test if you see anybody on c.n.n. or m s n b c or in the Democratic Party question the f.d.a. decision in any way all they are doing is politicizing this issue and at a cost of American lives we cannot afford in this China virus debate to politicize or therapeutics in convalescent class by me if that's

like going after Bambi you know this is the most one of the it's proven safe and effective Thank you all right. I'm a huge. Moment. For. You.

Is late in our judgment where we've been trying to do this for weeks simply with. I'm not I'm not I'm not privy to what the decisions were and what the data there was I haven't looked at that but I can I again I tell you this convalescent plasma is not on controversial it's been used for decades across many diseases. The odds of it hurting you are close to 0 the odds of it helping you are close to 100 percent this is the right to try president this is a time when Americans are dying and this is something that can be useful and so so look this timing issue again I think I think it's a way of people trying to politicize what shouldn't be politicized...

2020-08-25 Dockser Marcus A: Science Behind Convalescent Plasma for Covid-19 is Clouded by Politics in FDA Authorization. The Wall Street Journal Aug 25, 2020. https://www.wsj.com/articles/fda-officials-reject-claims-that-convalescent-plasma-decision-was-politicized-11598362563?mod=article_inline

XI. In October 2020, President Trump, former New York Mayor Rudy Giuliani, former New Jersey Governor Chris Christy, and former HUD Secretary Ben Carson, M.D. all contracted COVID-19. All were given immunotherapy IMMEDIATELY in the form of monoclonal antibodies or monoclonal antibody cocktails and the antiviral Remdesivir. At the time, President Trump's physicians kept reiterating the combination of an immunoglobulin and antiviral were EXPERIMENTAL when for the last century some form of immunoglobulins and antivirals are SYNERGISTIC and should be the STANDARD of CARE.

2020-10-02 Homer M: Timeline: What we know about Regeneron"s antibody cocktail that was given to President Trump. (Ref 602). https://www.khou.com/article/news/health/coronavirus/trump-regeneron-polyclonal-antibody-cocktail/285-636b1f14-fed2-42f3-8b41-0a565a2dd967

They are "a real best chance of being a game changer," NIH Director Francis S. Collins told the Washington Post about the experimental drug.

2020-10-05 Philippidis A, LeMieux J: Trump's treatments: Regeneron's antibodies and Gilead's Remdesivir explained. Genetic Engineering & Biotechnology News. (Ref 603) https://www.genengnews.com/insights/trumps-treatments-regenerons-antibodies-and-gileads-remdesivir-explained/

2020-10-05 LaMonica PR: Trump has ties to drugmaker Regeneron – and now its stock is surging. CNN Business. (Ref 604) https://www.cnn.com/2020/10/05/investing/trump-regeneron/index.html

New York (CNN Business)President Trump received a high dose of an experimental antibody cocktail from Regeneron as part of his Covid-19 treatment.

Now the drugmaker's stock is up sharply -- and questions are swirling about the president's ties to Regeneron's <u>billionaire CEO</u>.

Trump's team revealed Friday that the president received the drug, called REGN-COV2, which is being used to alleviate symptoms and reduce viral load. Shares of Regeneron surged 7% Monday, bringing the stock's year-to-date gain to more than 60%. The stock reached its highs of the day after Trump tweeted that he will be leaving the hospital Monday evening.

Regeneron CEO <u>Dr. Leonard Schleifer</u> and President Trump are acquainted: The CEO has been a member at <u>Trump's golf club in Westchester</u>, New York, and his company also <u>received \$450 million in government funding in July</u> as part of the president's <u>Operation Warp Speed</u> plan to quickly develop a vaccine and other treatments for Covid-19.

Meanwhile, Trump also recently owned shares of Regeneron (<u>REGN</u>) -- as well as Gilead Sciences (<u>GILD</u>), maker of the antiviral drug remdesivir that the <u>president is also taking</u>. Both stocks were listed as assets on Trump's <u>2017 filing with the U.S. Office of Government Ethics</u>, though neither were holdings on the president's <u>most recent filing for 2020</u>.

"Len and President Trump are acquaintances from both living in the Westchester area for many years but didn't have any regular contact until this year, when they've discussed matters around Covid on occasion," Regeneron told CNN Business in a statement.

According to Forbes, Schleifer is <u>now worth \$2.5 billion</u>, up from \$2.1 billion in the middle of March. Schleifer <u>primarily donated to Democratic political candidates and PACs</u> in the 2016 and 2018 elections, according to Federal Election Commission records

Regeneron is one of many biotechs and Big Pharma firms that has skyrocketed on hopes that it may be able to quickly develop an effective coronavirus treatment. The company <u>started human trials</u> for its antibody cocktail in June and <u>began a phase 3 trial</u> just a month later.

It has not yet been approved by the Food and Drug Administration, however. The FDA can approve the administration of it through so-called compassionate use requests on an individual basis. Regeneron confirmed to CNN Business that one of the president's doctors made such a request to Regeneron and the FDA to approve administering the drug to Trump.

Schleifer defended the decision to give Trump the cocktail last week, telling CNN's Wolf Blitzer that Trump "is in a higher-risk group for a variety of reasons" and that "we hope that we will give his immune system enough of a boost so that he can win this and make a complete recovery."

"We've got a lot of data, but we're still in the experimental phase. But when you're in the midst of a pandemic and you have people at risk, we think it makes sense to try these," Schleifer added.

Regeneron added in its statement to CNN Business that it is "in discussions with the FDA about potential for an Emergency Use Authorization for REGN-COV2" following the release of positive data about the drug last week.

The company had <u>announced</u> just a few days before President Trump's admission to Walter Reed that its cocktail "reduced viral load and the time to alleviate symptoms in non-hospitalized patients."

Regeneron said it is also in the process of studying the effect of the cocktail on hospitalized patients, as well as whether it can prevent infection in people who have been exposed to Covid-19.

Dr. George Yancopoulos, Regeneron's president and chief scientific officer, told CNN's Julia Chatterley in an interview Monday that the company is hoping it can get

more doses of REGN-COV2 to patients within the next few months thanks to a partnership with Big Pharma giant Roche.

"We are on track to deliver 300,000 doses by the end of the year and...produce 300,000 doses a month while the demand may even still exceed that," Yancopoulos said. "If the drug is really working and having the effects that we all hope it would, it could be doing a lot of good for a lot of people."

Correction: An earlier version of this story misstated the compassionate use request process. One of the president's physicians made the request to Regeneron and the FDA

2020-10-05 Cohen J: Update: Here's what is known about Trump's COVID-19 treatment. Science. (Ref 605) https://www.sciencemag.org/news/2020/10/heres-what-known-about-president-donald-trump-s-covid-19-treatment

2020-10-05 Gringlas S, Sprunt B: Timeline: What we know of President Trump's COVID-19 diagnosis, treatment. NPR. (Ref 606).

 $\frac{https://www.npr.org/sections/latest-updates-trump-covid-19-}{results/2020/10/03/919898777/timeline-what-we-know-of-president-trumps-covid-19-diagnosis}$

XII. The Scientists of both *Regeneron* and *Eli Lilly* recognized from their Clinical Trial data that the late administration of their monoclonal antibodies were not as effective as **EARLY** (**WITHIN 72-96 HOURS of diagnosis**). Therefore, in the applications for the EUAs for both Regeneron's monoclonal antibody cocktail (two monoclonal antibodies) and Eli Lilly's monoclonal antibody, it was requested that it be stipulated that the monoclonal antibodies would be for outpatient use but in a hospital-like setting for mild-to-moderate COVID-19 patients ONLY and not to be used for severe disease requiring respiratory support and ICUs. **They suggested that patients with severe COVID-19 should be relegated to COVID-19 Convalescent Plasma treatment**:

2020-10-07 Loftus P: Eli Lilly asks FDA to authorize Covid-19 antibody Drug. Wall Street Journal, Updated October 7, 2020, 11:31 pm ET. (Ref 611) https://www.wsj.com/articles/eli-lilly-asks-fda-to-authorize-covid-19-antibody-drug-11602074998

If cleared for use, the drug could be the first to treat less severe cases of Covid-19. The few other therapies authorized for Covid-19 treatment, including remdesivir from <u>Gilead Sciences</u> Inc. GILD 1.41% and <u>convalescent plasma</u>, target hospitalized patients with more serious cases.

Lilly said it would seek authorization for use in higher-risk patients to prevent their recently diagnosed mild-to-moderate disease from worsening to a severe state. Executives of the Indianapolis-based company said higher-risk groups may include people 65 years of age or older or obese patients.

"Anything that helps with preventing hospitalization and preventing progression is going to be a big advance," Rajesh Tim Gandhi, an infectious-disease physician at Massachusetts General Hospital and Harvard Medical School, said in an interview.

Lilly's antibody drug could also be the first in a new class of Covid-19 agents that not only might provide treatment but also potentially give temporary protection against the virus to people at risk of infection. That would <u>fill a gap until vaccines</u> <u>are authorized</u>, though people may need to take the antibody drugs more than once to sustain the protection.

"When we started this project we always believed that vaccines would be a longterm solution but that antibodies could come to patients faster," Lilly research head Daniel Skovronsky said in an interview. "We can make them faster, test them faster."

The leading experimental antibody drugs have shown enough promise in testing so far that President Trump was <u>given one</u> developed by <u>Regeneron</u> Pharmaceuticals Inc.

Regeneron said Wednesday night it has asked the Food and Drug Administration to authorize use of its antibody drug cocktail for Covid-19. The company said it has supply for 50,000 patients available and will have 300,000 within a few months.

Lilly said last month its drug reduced the rate of hospitalization compared with a placebo in a study. About 1.6% were hospitalized or visited the emergency room for Covid-19 after being injected with the drug, compared with 5.8% of people who didn't get the drug in the study

2020-10-07 Gumbrecht J, Howard J: Eli Lilly seeks EUA from FDA to Covid-19 antibody treatment. CNN Health. The 3 minute 42 second video attached to this article is the most succinct overview of antibody therapies that should be employed in the treatment of COVID-19 regarding both **Passive Immunization** [the early administration of exogenous neutralizing antibodies to individuals (<72 hours of COVID-19 detection or prophylactically)] and **Active Immunization** [vaccination of an individual which is prevention after the ~ 2-3 week increasing development of neutralizing antibodies in the uninfected individual). (Ref 612). https://www.cnn.com/2020/10/07/health/eli-lilly-antibody-therapy-results-eua/index.html

2020-10-08 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil A, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh Myoung-don, Ruiz-Palacios GM, Benfield T, Fatkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Bergess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC, for the ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 – Final Report. NEJM.org, October 8, 2020. Published in harcopy N Engl J Med 2020; 383:1813-1826. November 5, 2020. A preliminary version of this article was published on May 22, 2020. (Ref 613) https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764.

SAFETY OUTCOMES

In the as-treated population, serious adverse events occurred in 131 of 532 patients (24.6%) in the remdesivir group and in 163 of 516 patients (31.6%) in the placebo group (Table S17). There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group

(15.5% of patients) (Table S19). No deaths were considered by the investigators to be related to treatment assignment.

Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group (Table S18); 41 events were judged by the investigators to be related to remdesivir and 47 events to placebo (Table S17). The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, and increased blood glucose level (Table S20). The incidence of these adverse events was generally similar in the remdesivir and placebo groups.

Given the preliminary results about remdesivir, the Food and Drug Administration issued an Emergency Use Authorization on May 1, 2020 (modified on August 28, 2020), to permit the use of remdesivir for treatment in adults and children hospitalized with suspected or laboratory-confirmed Covid-19. Remdesivir has also received full or conditional approval in several other countries since that time. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients. Current strategies are evaluating remdesivir in combination with modifiers of the immune response (e.g., the Janus kinase [JAK] inhibitor baricitinib in ACTT-2, and interferon beta-1a in ACTT-3). A variety of therapeutic approaches including novel antivirals, modifiers of the immune response or other intrinsic pathways, and combination approaches are needed to continue to improve outcomes in patients with Covid-19.

- Mr. President, in late November 2020, I had elderly, debilitated in-patients with XIII. newly diagnosed urgent surgical problems (and now tested POSITIVE for COVID-19 when within the previous week they had been negative) admitted to the Unit II General Surgery (SLU) division, Surgical Service (112-jc), St. Louis VAMC of which I was the Chief Attending General Surgeon-of-Record. Knowing the FDA recommended (by non-proclamation or omission) for EARLY administration (within 72-96 hours) of Remdesivir (August 28, 2020) and COVID-19 Convalescent Plasma (September 2, 2020), I immediately requested my residents write orders for both: a five-day course of Remdesivir and an infusion of COVID-19 Convalescent Plasma (CCP). Each of the patients received the one infusion of CCP without any difficulty. BUT, by the second dose of Remdesivir, the Chief of Infectious Diseases had ordered the Pharmacy to stop the continuation of the orders for Remdesivir citing the VACO directive of November 2020 which you will see follows. By the way, the treated individuals had NO symptoms after their complete treatment with CCP and one dose of Remdesivir:
 - 1. On October 22, 2020, Remdesivir (Velkury) was designated by the FDA as a new prescription drug, NDA 214787.

 $\underline{https://www.accessdata.fda.gov/drugsatfda\ docs/appletter/2020/214787Orig1s000ltr.pdf}$

- **2.** In November 2020, the VA Pharmacy Benefits Management Services 10PAP, Medical Advisory Board, and VISN Pharmacist Executives **must not have read**
- 0.1 2022-09-11 Dear Mr. President Case Report EDIT 9-22-2022

Rear Admiral Hinton's 8/28/2020 revision of the EUA regarding Remdesivir https://web.archive.org/web/20200829175858/https://www.fda.gov/media/137564/download and they thus based the Inclusion Criteria on the EUA of May 1, 2020:

Inclusion Criteria

The following must be fulfilled to meet criteria for remdesivir Hospitalized with **SEVERE** COVID-19 (room air oxygenation saturation <94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is invasive or non-invasive ventilation or ECMO)***

https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf This URL cannot be found today even with the Internet Archive which suggests that the VA removed the discoverability of this incorrect (WRONG) directive:

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS PAST COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information

Exc	clusion Criteria
	answer to ANY item below is met, then the patient should NOT receive remdesivir Treated for COVID-19 as an outpatient AST or ALT > 5 times the upper limit of normal
	Hospitalized patients but NOT requiring supplemental oxygen* Concomitant use of hydroxychloroquine or chloroquine Current eGFR < 30 mL/min**
Inc	lusion Criteria
The fo	ollowing must be fulfilled in order to meet criteria for remdesivir
	Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
Su	pplemental Information
or wh	nmended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving o remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration rapy has not been given
	haspitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be icated on a case by case basis
recom espe	ents with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not amended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, cially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on guidance.
	emdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with
cortico	steroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19
Prena	red: November 2020, Contact: Kelly Echevarria, PharmD, BCPS, AO-ID, BCIDP, National Clinical Pharmacy Program

Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P

Updated version may be found at PBM INTERnet or PBM INTRAnet

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Mr. President, ironically while CCP was under an EUA, VELKURY (Remdesivir) had become a prescription drug (NDA 214787) on October 22, 2020. Mr. President, unfortunately, NO ACCOUNTABLE PARTY IN <u>VA CENTRAL</u> <u>OFFICE</u> seems to have ever read the revised EUAs of Remdesivir of August 28, 2020, or after up to October 22, 2020, nor the New Drug Application NDA# 214787 of October 22, 2020.

(Mr. President, I assume the nominal responsible parties of the above directive--which cannot be found on the Internet were: (1.) the VA Pharmacy Benefits Management Services, (2.) the VA Medical Advisory Panel, and (3.) VISN Pharmacist Executives. In December 2020, I contacted by e-mail VHA Chief Medical Executive Richard Stone, M.D. (It was stated that he had the authority of the VHA Under Secretary of Health) and the following correspondence ensued:

2020-12-13 2020-12-13 Andrus CH: Letter to the Editor of the New England Journal of Medicine regarding treatment with and synergy of *Passive Immunization* regarding the SARS-CoV-2 virus infection. ***The editors of NEJM ignored the letter but on January 6, 2021 published the landmark article (appropriately age stratified and COVID-19 Convalescent Plasma given within 72 hours of diagnosis): Libster, et. al.: Early high-titer plasma therapy to prevent severe Covid-19 in older adults, ClinicalTrials.gov, NCT04479163. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2033700, January 6, 2021, 1-9. (Ref 691) https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true

2020-12-20 Andrus CH: E-mail submitted to Dr. Richard Stone, M.D., Chief Medical Executive (acting Under Secretary of the Veterans Health Administration), regarding the WRONG INCLUSION CRITERIA which contradicted the FDA directive of early administration in the course of COVID-19 disease (<72 hours from diagnosis) going forward from August 28, 2020 to the present, regarding Remdesivir (an FDA -approved licensed drug: NDA# 214787). This ERRONEOUS DIRECTIVE was still published on the Internet as of October 3, 2021—not having been retracted by the Veterans Health Administration (VHA)—SHAME ON THE VHA! The URL is no longer available.

https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf What use to be at this U.S. Department of Veterans Affairs website is the following page that directed the administration of Remdesivir at the wrong time.

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making to standordize and improve the quality of patient care, and to promote cost-effective drug prescribing THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL SCONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

iee the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.
Exclusion Criteria
f the answer to ANY item below is met, then the patient should NOT receive remdesivir Treated for COVID-19 as an outpatient AST or ALT > 5 times the upper limit of normal Hospitalized patients but NOT requiring supplemental oxygen* Concomitant use of hydroxychloroquine or chloroquine Current eGFR < 30 mL/min**
Inclusion Criteria
The following must be fulfilled in order to meet criteria for remdesivir Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase fro baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
Supplemental Information
Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full durati of therapy has not been given
Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should l adjudicated on a case by case basis
*Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the rie especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based olocal guidance. ***Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with articosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19
Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program

Updated version may be found at PBM INTERnet or PBM INTRAnet

Manager, VA Pharmacy Benefits Management Services 10P4P

2020-12-24. Andrus CH: E-mail directed to the New England Journal of Medicine, the Veterans Health Administration, etc. It was ignored!

The following reference published on **January 6, 2021**, in *The New England Journal* of Medicine (NEJM) has gone unnoticed due the news disruption by the Insurrection of January 6, 2021. This was a landmark Randomized Control Trial from Argentina that demonstrated that when aged matched, COVID-19 Convalescent Plasma decreased significantly morbidity and decreased mortality but was not significant (due to the small size of the study).

2021-01-06 Libster R, Pérez Marc, Wappner D, Coviello S, Bianchi A, Braem V, Esteban I, Caballero MT, Wood C, Berruetta M, Rondan A, Lescano G, Cruz P, Ritou

0.1 2022-09-11 Dear Mr. President Case Report EDIT 9-22-2022

This submission is NOT for financial gain but for educational purposes only for ALL the American people

Y, Fernández Viña V, Alvarez Paggi D, Esperante S, Ferreti A, Ofman G, Ciganda A, Rodriguez R, Lantos J, Valentini R, Itcovici N, Hintze A, Oyarvide ML, Etcegarary C, Neira A, Name I, Alfonso J, López Castelo R, Caruso G, Rapelius S, Alvez F, Etchenique F, Dimase F, Alvarez D, Aranda SS, Sánchez Yanotti C, De Luca S, Baglivo J, Laudanno S, Nowogrodzki F, Larrea R, Silveyra M, Leberzstein G, Debonis A, Molinos J, González M, Perez E, Kreplak N, Pastor Argüello S, Gibbons L, Althabe F, Bergel E, Polack FP, for the Fundación INFANT-COVID-19 Group*: Early high-titer plasma therapy to prevent severe Covid-19 in older adults, ClinicalTrials.gov, NCT04479163. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2033700, January 6, 2021, 1-9. (Ref 707) https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true Republished N Engl J Med, February 18, 2021; 384(7): 610 – 618.

2021-01-24 Face the Nation: Margaret Brennan interviews Deborah Birx, M.D. Face the Nation, CBSNews. The abridged version that aired on Face the Nation on Sunday morning, January 24, 2021: https://www.youtube.com/watch?v=odklJGnhvhU The complete interview of Dr. Birx by Margaret Brennan of Face the Nation of CBSNews: https://www.youtube.com/watch?v=nW41YylWipM (Ref 730)

2021-02-01 Andrus CH:

(Ref 738)

Dear Dr. Birx:

On March 24, 2020, while there was much discussion and debate about COVID-19 convalescent plasma and the possible development of monoclonal antibodies against COVID-19, U.S. Medicine and the Government failed to explain to the American public the differences and individual utilities of *Active Immunization* (vaccines to stimulate patient antibody production) and *Passive Immunization* (provision of convalescent plasmas, convalescence sera, and immunoglobins from other species providing already formed antibodies (IgM, IgG, and IgA) against the virus in COVID-19 immunologically naïve patients immediately within 72 hours of diagnosis (testing positive).

In your interview with Margaret Brennan, you stated the following:

DR. BIRX: Well, what I do know and what was reassuring to me all along is I knew this would be studied. I knew that the emails, the reports that I wrote, the request to expand testing, the **how to improve therapeutics**, all of that, all of that would eventually come to light. Maybe not in my lifetime.

Last summer you stated that we should collect 500,000 units of convalescent plasma to prepare for the spike in the Fall –well, we as a nation didn't do that. In fact, as you

are a clinical Immunologist, you are very well aware of *Passive Immunization* in the initial early treatment (<72 hours) with the contraction of or exposure to a disease without any true alternate therapy as soon as possible (<72 hours) [e.g.: rabies, hydrops fetalis (Rhogam within 72 hours to an Rh negative mother at delivery of the prior pregnancy, snake bites, etc]. In fact, to withhold *Passive Immunization* (RhoGAM) from a newly delivered Rh negative mother is considered malpractice. By semantics and legal obfuscation, over the course of the last 10 months, the American public has been led down the rabbit hole by the Medical and Research community, the "Industry", and the Federal Government by not officially providing any timely-appropriate immunotherapy in the treatment of COVID-19 positivity with *Passive Immunization* until recently:

- 1. In March 2020, the FDA declared COVID-19 Convalescent Plasma *Investigational* instead of a *Biosimilar* biologic;
- 2. On March 24, 2020 the FDA outlined *Eligibility Criteria* in the <u>late treatment of severe COVID-19 disease</u> with COVID-19 Convalescent Plasma (at deaths door when the viremia is not the cause of death but rather the SARS pathophysiology) justifying this choice of late administration as the <u>US did not have enough</u> recovered convalescent patients (>14 days);
- 3. In early April 2020, the Mayo Clinic with the FDA offered COVID-19 Convalescent Plasma in the Expand Access protocol Convalescent Plasma COVID-19 (Coronavirus) Treatment (uscovidplasma.org) using the at-deathsdoor *Eligibility Criteria* ("expanded access" is really "compassionate use"—so, therefore, any resultant data cannot officially be used for completion of a Phase I Clinical Trial). Over 94,000 units of COVID-19 plasma were given AT THE THERAPEUTICALLY WRONG TIME only to severely-effected patients with the SARS pneumonitis or MSOF.
- 4. Throughout the last 11 months, the DHHS through the FDA and NIH has equated Safety Trials (Phase I trials) with Efficacy Trials (Phase II/III) so that there are no "Completed" Phase I (safety) trials with regards to COVID-19 biologics. Who should explain to the American people if the NIH plans on evading *ad infinitum* the "Right to Try" Law PL-115-176? Has not **a bad** precedent been set by not declaring a "completed" Phase I Trial with regards to COVID-19 Convalescent Plasma? Will any NIH protocol or FDA new drug/biologic Phase II/III trial and in any future research not be required to abide by the "Right to Try" Law, PL-115-176? In essence, the FDA and NIH are in violation, at least in violation of the intent of federal law PL-115-176 which requires a "Completed" Phase I Trial only for application of PL-115-176. Forcing patients to participate in Placebo-controlled Phase II/ III Trials is coercion which is prohibited by every IRB in the nation. On August 12, 2020 in the St. Louis Post-Dispatch, the following quote involving one of the FDA-Mayo Clinic's named investigators was documented:

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?"

https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article_ccec0f56-4493-5a26-8601-45e35d364b2d.html

No IRB, worth their salt, should ever approve of such a concept of coercion in any Clinical Trial; and the FDA should not only shut down any Clinical Trial with such flagrant coercion but also censure, if not shut down, any IRB that permitted such coercion.

5. All summer, the FDA kept announcing they were close to releasing an EUA regarding COVID-19 Convalescent Plasma. President Trump went to the American Red Cross at the end of July confirming the need in his mind and that of the President's COVID-19 Taskforce for COVID-19 Convalescent Plasma. The announcement of the EUA was delayed until it would be announced on Sunday, August 23, 2020, by President Trump on the eve of the Republican National Convention. The next day, the NIH COVID-19 Guidelines Panel condemned the EUA for lacking scientific rigorous analysis (being based on Expanded Access/Compassionate Use protocol data from the FDA/Mayo clinic study). In the most-recent guidelines of the NIH COVID-19 Guideline Panel of January 14, 2021, the NIH COVID-19 Guidelines Panel is now hedging its bets by hiding under "Convalescent Plasma" Last Update October 9, 2020:

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

(While the Mayo Clinic's Expanded Access Program (EAP) did not have an official "untreated control arm" since it was *Compassionate Use* only, the Mayo Clinic's EAP Safety Update in June 2020 of 20,000 patients actually included a total of 21,987 infused patients with 1,987 patients not completing

the post-infusion 7-day period and 8,130 being untreated. When one back-calculates varying the possible mortality rate in this untreated group, a mortality rate of 8.7% or greater would have been statistically significant with less than a 0.05% confidence level. *But, unfortunately, the Mayo Clinic's Expanded Access Program* did not even qualify as a "Completed Phase I Study" by the "purism" semantics of the NIH. Dr. Birx, the FDA has final statutory say over all new drugs and biologics, **NOT** the NIH.)

- 6. The Chief Scientist of the FDA, Rear Admiral Hinton, finally removed the severity criteria by removing completely the *Eligibility Criteria* regarding Remdesivir on August 28, 2020 (the VA Central Office pharmacy formulary panel was still insisting on the severity *Eligibilty Criteria* as the only criteria for those eligible for Remdesivir in November 2020--three months after it was rescinded by Rear Admiral Hinton). Veklury (remdesivir) EUA Letter of Approval, reissued 10/22/2020 (fda.gov)
- 7. On September 2, 2020, the FDA removed completely without public awareness the severe disease *Eligibility Criteria* for COVID-19 Convalescent Plasma. Many institutions are still applying the severe disease *Eligibility Criteria* to this day--thus refusing patients COVID-19 Convalescent Plasma treatment when they first become COVID-19 positive and present to the local ER—including recently a patient with a 104 fever and uncontrollable cough that I personally know. (i.e.: The FDA's complete removal of the *Eligibility* Criteria after September 2, 2020 can be demonstrated by viewing an example of the U.S. Food & Drug Administration's website: Recommendations for Investigational COVID-19 Convalescent Plasma by comparing the most recent URL: https://www.fda.gov/vaccines-blood-biologics/investigationalnew-drug-ind-or-device-exemption-ide-process-cber/recommendationsinvestigational-covid-19-convalescent-plasma by copying and pasting the URL into the Internet Archive (Wayback Machine) and displaying a URL before September 2, 2020 in which the severe disease *Eligibility Criteria* was outlined from April 2020 to September 2, 2020: Recommendations for Investigational COVID-19 Convalescent Plasma | FDA (archive.org):

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment ProtocolExternal Link Disclaimer. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - O Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
 - lung infiltrates > 50% within 24 to 48 hours
 - O Life-threatening disease is defined as one or more of the following:

- respiratory failure,
- septic shock,
- multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.
- 8. Before the EUAs were issued by Rear Admiral Hinton regarding the Regeneron monoclonal cocktail (casirivimib and imdevimab) and Eli Lilly monoclonal antibody bamlanivimib, on October 26, 2020 Eli Lilly asked the FDA to exclude the use of their monoclonal antibody in patients with any signs of severity of associated illness parameters such as any new requirement of oxygen supplementation in any non-COPD patient or increase in amount of oxygen supplementation in COPD patients.
- 9. Rear Admiral Hinton issued EUAs for Eli Lilly's bamlanivimib (https://www.fda.gov/media/143602/download) on November 10, 2020 and for Regeneron's casirivimib and imdevimab on November 21, 2020 (https://www.fda.gov/media/143891/download). Both EUAs state the following (I will use the Regeneron's monoclonal cocktail as the example as President Trump had received this "experimental" cocktail in early October 2020 prior to the issuing of these EUAs):

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized casirivimab and imdevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply casirivimab and imdevimab to authorized distributor(s)4, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities, as needed:
- The casirivimab and imdevimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
- Casirivimab and imdevimab may only be administered together;
- \bullet Casirivimab and imdevimab is not authorized for use in the following patient populations 5 :
 - Adults or pediatric patients who are hospitalized due to COVID-19,
 - Adults or pediatric patients who require oxygen therapy due to COVID19, or
 - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.
- Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion

reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- The use of casirivimab and imdevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.
- 10. On November 24, 2020, in *NEJM* was published: Simonovich VA, *et al*: A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia (nejm.org) which is an outstanding, well-thought-out prospective trial using the discontinued/withdrawn severely-ill COVID-19 patient *Eligibility Criteria* in which all COVID-19 Convalescent Plasma was given only in patients with severe COVID-19 SARS pneumonitis. Unfortunately, the authors failed to mention in their paper's abstract conclusion that the outcome of the study was based on patients given COVID-19 Convalescent Plasma with only severe SARS pneumonitis—following the previously omitted (September 2, 2020) severe patient *Eligibility Criteria* in which *Passive Immunization* was administered at the WRONG TIME—that is at deaths-door instead of within 72-hours of COVID-19 positivity!:

CONCLUSIONS

No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. (PlasmAr ClinicalTrials.gov number, **NCT04383535. opens in new tab.**)

11. I wrote a Letter to the Editors of *The New England Journal of Medicine* (*NEJM*) regarding Simonovich VA, *et al* and included those I could access with regards to e-mails in the DHHS, the VA, and Saint Louis University SOM as I am a Professor of Surgery and the General Surgery Residency site director at the St. Louis (John Cochran) VAMC. I never got a response back from the *NEJM* but on January 6, 2021, the landmark article by Libster R, *et al*: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) demonstrated a statistically significant decrease in mortality and severity of illness in a specific age group (the elderly) when COVID-19 Convalescent Plasma was given within 72 hours (AT THE RIGHT TIME) of detection of COVID-19 positivity. As is stated in the conclusion of the abstract in this article:

CONCLUSIONS

Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19. (Funded by the Bill and Melinda Gates Foundation and the Fundación INFANT Pandemic Fund; Dirección de Sangre y Medicina Transfusional del Ministerio de Salud number, PAEPCC19, Plataforma de Registro Informatizado de Investigaciones en Salud number, 1421, and ClinicalTrials.gov number, NCT04479163.)

One of my fellow Attending Surgeons at the VA came to my office after my e-mail cover letter to my Letter to the Editors to *NEJM* and stated that I had every right under the first Amendment to communicate whatever I wished but I was just making a fool of myself as there were much smarter people than me involved in setting standards for COVID-19 therapy. The next night, I got a call from an administrator at Saint Louis University SOM (SLUSOM) stating I was only allowed to speak about COVID-19 Convalescent Plasma with other faculty members of SLUSOM and the physicians, nurses, and other healthcare personnel at the local VA--St. Louis (John Cochran) VAMC and to STOP calling Washington DC. He then asked me unknowingly why I had included e-mails to Harvard. I responded that this e-mail was concerned my cover letter regarding my letter to the Editors of *The New England Journal of Medicine*. He responsed: Oh—speak only with those in the local VA and Saint Louis University.

[Please note I attached a slide of mortality due to COVID-19 by age range between March and November 2020. First, the mortality percentages by age range had not changed over those 9 months suggesting the USA has not diminished the death rate by any therapy employed so far in any age group over 40 years of age. Second, you will note, the mortality from 40 to 90 years increases by 0.67% per year: y = 0.0067x - 0.2647, $R^2 = 0.9676$; and, below age 40, the mortality rate increases only by 0.04% per year to maximally 0.12%/year: y= 0.0004x - 0.0023, R = 0.7987. Once again, as the mortality rates in all range groups over the age of 40 have not changed over the last 10 months, the late administration of *Passive Immunization* to the majority of the hundred thousand patients that received COVID-19 Convalescent Plasma was given at the WRONG TIME using the now rescinded FDA patient *Eligibility Criteria*--such administration at the WRONG TIME did not make a substantial impact. What this also implies is that sending the children and young adults back to in-school-learning will be relatively safe for the children—mortality rate 0.04% increase per year when compared with adults over age 40 years—mortality rate 0.67% per year (which is 16x higher than in children). This presents the possibility to generate a vector repository in our children who could then transmit COVID-19 to their parents, grandparents, and other adults who have a higher risk of severity of disease and death.]

12. The *NEJM* landmark article of January 6, 2021 by Libster R, *et al*: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) was overshadowed by the events that occurred later in the day in Washington D.C. Ironically, on January 14, 2021, *USA Today* ran an article: Rodriguez A: US officials urge Americans to ask their doctors about monoclonal antibodies for COVID. But is it too little, too late? Monoclonal antibodies for COVID in full supply, but lack demand: HHS (usatoday.com). On January 17, 2021 in *Infection Control* Today, Kavanagh K: As Vaccine Rollout Stalls, Move Monoclonal Antibodies Into COVID Fight

(infectioncontroltoday.com) using monoclonal antibodies used prophylactically to protect in exposures. **Both** monoclonal antibodies and COVID-19 Convalescent Plasma are **Passive Immunization** therapeutic agents and should therefore be administered at the same appropriate time-12 hours from symptomatology or COVID-19 positivity instead of only to patients at deaths-door. Over the last 10 months, the American public has been so misdirected (or lied to) by the ambiguity in the terminology and focus on vaccine production that few realize that **Passive Immunization** includes polyclonal antibodies (COVID-19 Convalescent Plasma) and monoclonal antibodies which should be given to all immediately when they become COVID-19 positive!

- 13. As is now being reported in the press, mutations of COVID-19 are developing around the World that may make the present vaccines and monoclonal antibodies ineffective.
- 14. As we go forth, the Standard-of-Care should be the following:
 - A. For those of the present 330 million Americans that are not yet infected (immunologically naïve to the disease COVID-19 negative), they should all be encouraged to receive one of the COVID-19 vaccines.
 - B. Every American who has had COVID-19 and is recovered by at least 14 days should be encouraged to donate COVID-19 Convalescent Plasma. https://www.aabb.org/for-donors-patients/give-blood
 - C. Every American who turns COVID-19 positive or becomes symptomatic (even if they have received a COVID-19 vaccine), should be afforded some form of *Passive Immunization* by the early-indisease treatment COVID-19 Convalescent Plasma/Sera or Monoclonal Antibiodies
 - D. As the COVID-19 mutations spread and the vaccines may be less effective, every American who turns COVID-19 positive or becomes symptomatic should be afforded *Passive Immunization* of COVID-19 Convalescent Plasma/Sera matching the COVID-19 mutation. Waiting for the development of a vaccine (or monoclonal antibodies) specific for the new COVID-19 mutation and withholding mutation specific COVID-19 Convalescent Plasma would be unconceivable and tantamount to patient abandonment. Every time the coronavirus mutates, it will take months to develop a new vaccine or a new monoclonal antibody—yet convalescent plasma effective against every next mutation will be available 14 days after the first human recovers from each new mutation of the coronavirus through plasmapheresis donation.

E. When Kidney Transplantation was considered *Investigational* in the 1960s and 1970s and the insurance industry would not pay for Kidney Transplantation as it was "Experimental", the Congress permitted for two decades the Attending Surgeons of Washington University SOM (Drs. Newton and Anderson) and Saint Louis University SOM (Drs. Maginn, Codd, and Garvin) to perform kidney transplants on both Veterans and civilians at the John Cochran (St. Louis) VAMC. Thus, the precedent six decades ago was set to employ the largest federal hospital system (both hospitals and CBOCs) in the nation of the Veterans Health Administration (VHA) to establish infusion centers to provide *Passive Immunization* in the treatment of COVID-19 for both Veterans and civilians.

F. Thomas Jefferson's replacement of John Locke's "property" with "the pursuit of happiness" in the *Declaration of Independence* was no mistake. We as American physicians should be leery of any potential inherent conflict-of-interest of *Industry's* and *Medicine's* working together possibly to the detriment of our patients. De facto, Medicine, the U.S. Government, and most of the World have publicly discredited polyclonal COVID-19 Convalescent Plasma (and Sera) while elevating monoclonal antibodies as viable early treatments in COVID-19 positivity—they are both *Passive Immunization* therapies. Every time the coronavirus mutates, it will take months to develop a new vaccine or a new monoclonal antibody—yet convalescent plasma effective against every next mutation will be available 14 days after the first human recovers from each new mutation of the coronavirus through plasmapheresis donation. The present situation throughout the World today is analogous to that of the mythological Sisyphus pushing the rock up the hill only for it upon nearing the top of the hill rolling back down for eternity.

After having viewed the abridged version of your interview on January 24, 2020 (Full interview: Dr. Deborah Birx on "Face the Nation" - YouTube) with Margaret Brennan, in my eyes you have throughout your professional life been a dedicated Military and Civil Service physician for individual patients and patients in the aggregate. Both you and I are professionally of the same generation. When we graduated, you from Penn State Univ SOM in 1980 and I in 1979 from Saint Louis Univ SOM, we both swore *Primum non Nocere* in the care of all of our patients throughout our future lives as physicians. As I viewed the interview last Sunday, I saw a physician who loves her country and has dedicated her life as a physician to bettering all patients' lives. It is your duty, my duty, and all physicians' duty by our oaths of *Primum non Nocere* to advocate for not just the <u>preventative</u> measures of *Active Immunization* but also all potential therapeutic measures of *Passive Immunization*.

It would be my hope that this correspondence will be your introduction to President Biden to explain your suggestions and thoughts on our future therapy—both Active Immunization and Passive Immunization -- for all Americans. As Dr. Fauci is the President's Chief Medical Advisor on the USA COVID-19 epidemic, I will forward this letter to him, the NIH, and the FDA to help facilitate your meeting with the President. My previous Letter to the Editor of The New England Journal of Medicine has not been published but was probably partially the impetus for the NEJM publishing on January 6, 2021-01-06: Libster R, et al: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) I will be sure to include the Editors of the New England Journal of Medicine in this correspondence today. Over the past year, I have submitted three items (listed below) to the U.S. Copyright Office of the Library of Congress to preserve the chronology of what has occurred for history. With any and all of my correspondence regarding our present COVID-19 epidemic, I will dutifully provide all that is asked of me by the U.S. Federal Government as it is my duty as a physician and surgeon of the Veterans Health Administration, U.S. Department of Veterans Affairs.

- 1. Andrus CH: *Time*: The Crucial Independent Variable of the COVID-19 Pandemic. U.S. Copyright Office, June 8, 2020. TXu002199029
- 2. Andrus CH: Mayo Clinic "Safety Update" should be Classified as a Completed Phase I Trial of COVID-19 Convalescent Plasma. July 22, 2020. TXu002214049
- 3. Andrus CH: 1 Dear Mr. President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. November 18, 2020. TXu002232947

On the evening of January 20, 2021, the America public was reminded of past Presidential inaugural addresses:

President Abraham Lincoln's 2nd Inaugural Address includes the lines that I, as a VA physician and surgeon, and we as Americans have promised:

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan; to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

That night, the most famous line of President Kennedy's was part of what was recited: "And so, my fellow Americas: ask not what your country can do for you—ask what you can do for you country." Dr. Birx, both you and I were in grammar school when the final lines were spoken that are most *apropos* to our present crisis and that for all time:

My fellow citizens of the world: ask not what America will do for you, but what together we can do for the freedom of man.

Finally, whether you are citizens of America or citizens of the world, ask of us here the same high standards of strength and sacrifice which we ask of you. With a good conscience our only sure reward, with history the

final judge of our deeds, let us go forth to lead the land we love, asking His blessing and His help, but knowing that here on earth God's work must truly be our own.

Dr. Birx: Godspeed.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine Chief, Unit II General Surgery (SLU GS division), St. Louis (John Cochran division) VAMC

Home: 314-455-9482; home e-mail: candrus600@aol.com

Beeper: 314-491-2417

My wife's, Pamela Bergkamp Andrus's, cell phone: 314-809-9634

Within 48 hours, Rear Admiral Denise Hinton, R.N., M.S., revised the EUA for COVID-19 Convalescent Plasma:

2021-02-02 U.S. Food & Drug Administration: CLINICAL MEMORANDUM, EUA 26382, COVID-19 Convalescent Plasma (CCP). NONE OF THE VERSIONS OF THESE MEMOs are dated and thus dating was obtained from the digital captures using the Internet Archive (WayBack Machine). The URL of this Memorandaum is: https://www.fda.gov/media/141480/download (Ref 739)

From September 1, 2020 to at least February 2, 2021 was the first <u>iteration/rough draft</u> to justify Hinton's reissuing the CCP EUA in November 2020 and then probably (the Wayback Machine has no digital captures from Feb 2 to Feb 15) the first major revision on February 4, 2021, of the CCP EUA of August 23, 2020 which was the first EUA regarding COVID-19 Convalescent Plasma issued by the FDA after the press conference announcement by President Trump of that day: Sunday, August 23, 2020—the day prior to the start of the Republican National Convention. Coincidentally, this six-month draft was the CLINICAL MEMORANDUM probably used to justify RADM Hinton's EUA of February 4, 2021 which was 48-72 hours after Dr. Andrus' Letter to Dr. Deborah Birx of February 1, 2021. As this first iteration of the MEMO regarding EUA 26382 was a draft, it lacks (1) the name of the individual who wrote it; (2) the name of the individual to whom it is written; and (3) the names of the FDA division chiefs through which the memo would pass. It does list the Sponsor, Robert Kadlec, M.D., to whom all EUAs previously have been issued regarding Remdesivir, Monoclonal Antibodies/Antibody Cocktails, and COVID-19 Convalescent Plasma (CCP).

https://web.archive.org/web/20210202143902/https://www.fda.gov/media/141480/download The Executive Summary of the CLINICAL MEMORANDUM of September 1, 2020 through at least February 2, 2021:

EXECUTIVE SUMMARY COVID-19 Convalescent Plasma (CCP), an unapproved biological product, is proposed for use under an Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act),(21 USC 360bbb-3) as a passive immune therapy for the treatment of hospitalized patients with COVID-19, a serious or life-threatening disease. There currently is no adequate, approved, and available alternative to CCP for treating COVID-19. The sponsor has pointed to four lines of evidence to support that CCP may be effective in the treatment of hospitalized patients with COVID-19: 1) History of convalescent plasma for respiratory coronaviruses; 2) Evidence of preclinical safety and efficacy in animal models; 3) Published studies of the safety and efficacy of CCP; and 4) Data on safety and efficacy from the National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.

Considering the totality of the scientific evidence presented in the EUA, I conclude that current data for the use of CCP in adult hospitalized patients with COVID-19 supports the conclusion that CCP meets the "may be effective" criterion for issuance of an EUA from section 564(c)(2)(A) of the Act. It is reasonable to conclude that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA. Current data suggest the largest clinical benefit is associated with high-titer units of CCP administered early in the course of disease. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient populations for its use.

Recommendation: CCP meets the eligibility criteria for EUA under section 564 of the Act.

February 15, 2021 was the first digital capture of the second interation to justify the ongoing EUAs of COVID-19 Convalescent Plasma (CCP) upgrades by RADM Hinton. As this second iteration of the MEMO regarding EUA 26382 does not seem to be a draft, it contains (1) the name of the individual who wrote it; (2) the name of the individual to whom it is written; and (3) the names of the FDA divisions chiefs through which the memo would pass. It does not list the Sponsor (not yet appointed by the Biden administration and confirmed) to whom all EUAs will be issued regarding Remdesivir, Monoclonal Antibodies/Antibody Cocktails, and COVID-19 Convalescent Plasma (CCP).

http://web.archive.org/web/20210215192634/https://www.fda.gov/media/141480/download The Executive Summary of the CLINICAL MEMORANDUM from February 15, 2021 to at least April 23, 2021 (the last digital capture by the WayBack Machine) to be unchanged:

EXECUTIVE SUMMARY

COVID-19 Convalescent Plasma (CCP) was granted Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19 on August 23, 2020. At that time, the totality of the scientific evidence supported a determination that the use of CCP in hospitalized patients with COVID-19 met the "may be effective" standard for issuance of an EUA, and it was reasonable to consider that the known and potential benefits of CCP outweighed the known and potential risks for the authorized use.

Following the EUA, emerging evidence from randomized controlled trials has continued to inform this assessment. The available evidence indicates that 1) the use of low titer CCP in hospitalized patients no longer meets the evidentiary standard of "may be effective", and 2) high titer CCP has not demonstrated benefit when administered late in the disease course in immunocompetent hospitalized patients.

Additional data from RCTs and observational studies support a determination that high titer CCP may be effective when administered early in the course of illness, particularly prior to the expected time of host antibody response. In patients with impaired humoral immunity, the potential therapeutic window may be prolonged. As RCT data continue to demonstrate that the risks of CCP do not exceed those observed with plasma transfusion in general, it is reasonable to believe that the known and potential benefits of use of high titer CCP outweigh the known and potential risks when used for the treatment of hospitalized patients with COVID-19, particularly early in the course of illness or in patients with impaired humoral immunity. Results from ongoing RCTs are expected to continue inform the optimal patient populations and product characteristics for efficacy of CCP in COVID-19.

Recommendation: The conditions of Emergency Use Authorization for CCP for the treatment of hospitalized patients with COVID-19 should be revised to exclude the use of low titer CCP. High titer CCP continues to meet criteria for Emergency Use Authorization for the treatment of hospitalized patients with COVID-19 early in the course of hospitalization. The letter of authorization and accompanying fact sheets should be revised to emphasize early administration of CCP in the absence of immunodeficiency or immunosuppression. Additional results from adequate and well-controlled trials will continue to be evaluated to further characterize the patient populations and product characteristics meeting EUA criteria.

2021-02-04 Hinton DM: U.S. Food and Drug Administration Letter to Nikki Bratcher-Bowman, Acting Assistant Secretary for Preparedness and Response, EUA-update regarding COVID-19 Convalescent plasma. February 4, 2021. (Please note that the position of Assistant Secretary of Preparedness and Response changed from February 2, 2021 (48 hours previous) from Robert Kadlec, M.D. who had been appointed by President Trump to an Acting Assistant Secretary for Preparedness and Response under the Biden Administration: Nikki Bratcher-Bowman.) (Ref 740) https://web.archive.org/web/20210218201225/https://www.fda.gov/media/141477/download

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19 (the virus was later named SARS-CoV-2). On March 27, 2020, on the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act, subject to the terms of any authorization issued under that section. On August 23, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with Coronavirus Disease 2019 (COVID-19), pursuant to Section 564 of the Act. On November 30, 2020, FDA reissued the August 23, 2020, Letter of Authorization to add a test acceptable to be used in the manufacture of COVID-19 convalescent plasma. Having concluded that revising this

EUA is appropriate to protect the public health or safety under Section 564(g)(2)(C) of the Act (21 U.S.C. § 360bbb-3(g)(2)(C)), FDA is again reissuing the Letter of Authorization in its entirety with revisions to: (1) include updates based on data from additional clinical trials; (2) clarify that the authorization is limited to use of only high titer COVID-19 convalescent plasma in hospitalized patients early in the course of disease and those hospitalized with impaired humoral immunity; (3) add the Abbott SARS-CoV-2 IgG test (ARCHITECT and Alinity i platforms), Beckman Coulter Access SARS-CoV-2 IgG test, EUROIMMUN Anti-SARS-CoV-2 ELISA (IgG) test, GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kit test, Kantaro COVID-SeroKlir test, Roche Elecsys AntiSARS-CoV-2 S test, and Siemens ADVIA Centaur SARS-CoV-2 IgG (COV2G) test as acceptable tests to be used for the purpose of qualifying high titer COVID-19 convalescent plasma in the manufacture of COVID-19 convalescent plasma; and (4) change the cutoff of the Ortho VITROS Anti-SARS-CoV-2 IgG test from S/C≥12.0 to S/C≥9.5 for qualification of COVID-19 convalescent plasma as high titer. COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. It is an investigational product and is not currently approved or licensed for any indication. The initial issuance of this EUA for COVID-19 convalescent plasma was based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the National Convalescent Plasma Expanded Access Protocol (EAP) sponsored by the Mayo Clinic. ⁵ Following the August 23, 2020 authorization, additional studies, including randomized, controlled trials, have provided data to further inform the safety and efficacy of COVID-19 convalescent plasma, and further characterize product attributes and patient populations for its use. Based on assessment of these data, potential clinical benefit of transfusion of COVID-19 convalescent plasma in hospitalized patients with COVID-19 is associated with high titer units administered early in the course of disease. ⁶ Transfusion of COVID-19 convalescent plasma in hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit. These considerations may be different in patients with suppressed or deficient humoral immunity. Therefore, this EUA is being revised to authorize only the use of high titer COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19, early in the disease course. The related fact sheets are revised accordingly. The use of low titer COVID-19 convalescent plasma is no longer authorized under this EUA.

It is reasonable to believe that the known and potential benefits of high titer COVID-19 convalescent plasma outweigh its known and potential risks for the treatment of patients hospitalized with COVID-19 early in the disease course. COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Given that the clinical evidence supporting this EUA remains limited, data from additional randomized, controlled trials are needed. Ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on the issuance of this updated EUA; providers are encouraged to enroll patients in those trials. Having concluded that the criteria for issuance of this authorization under 564(c) of the Act are met, I am authorizing the emergency use of high titer COVID-19 convalescent plasma for treatment of hospitalized patients with COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

2021-02-04 U.S. Food & Drug Administration: FDA in Brief: FDA Updates Emergency Use Authorization for COVID-19 Convalescent Plasma to Reflect New Data, February 4, 2021. This is deliberate legal obfuscation on the part of the FDA by stating that it was limiting authorization-- de facto, the FDA was really expanding authorization by appropriately limiting the EUA for COVID-19 Convalescent Plasma to "early in the disease course" which was contrary to FDA directives from March 24, 2020 to September 2, 2020 when the criteria was that CCP could only be given to severe patients late in the disease course. The provision of CCP late in the disease course was de facto perpetuated by the fact that the FDA had unobtrusively removed the strict severity of illness criteria late in the disease course from all FDA documentation by overwriting on September 2, 2020 and going forward on all subsequent documentation and not announcing it officially to the U.S. Medical and Research Community, probably the rest of the Federal Government, and most definitely not to the American people. The "high dose" vs "low dose" concern is a secondary issue—that was used as a distraction by the FDA--as with monoclonal antibodies/antibody cocktails, COVID-19 Convalescent Plasma and monoclonal antibodies are all *Passive Immunization* and are therapeutically identical if given EARLY IN THE COURSE OF THE DISEASE. https://www.fda.gov/newsevents/fda-brief/fda-brief-fda-updates-emergency-use-authorization-covid-19-convalescent-plasma-reflect-(Ref. 741) new-data

The following quote is attributed to **Peter Marks, M.D., Ph.D., Director of FDA's Center for Biologics Evaluation and Research**:

"The FDA is issuing a revision of the Emergency Use Authorization (EUA) for COVID-19 convalescent plasma as a result of our evaluation of the most recent information available. Based upon data from new clinical trials analyzed or reported since the original EUA was issued in August 2020, we have revised the EUA to limit the authorization to the use of high titer COVID-19 convalescent plasma for the treatment of hospitalized patients early in the disease course. This and other changes to the EUA represent important updates to the use of convalescent plasma for the treatment of COVID-19 patients.

"Issuance of, and updates to, EUAs are based on a thorough evaluation of currently available scientific evidence about medical products. In this case, as additional scientific evidence about COVID-19 convalescent plasma emerged, we revised the EUA to reflect the updated evidence. COVID-19 convalescent plasma used according to the revised EUA may have efficacy and its known and potential benefits outweigh its known and potential risks."

2021-02-05 Dockser Marcus A: FDA Limits Use of Convalescent Plasma as Covid-19 Treatment. Agency to scale back authorization of the antibody-rich blood component after studies yielded mixed results. The Wall Street Journal Feb 5, 2021. (Ref 746). https://www.wsj.com/articles/fda-limits-use-of-convalescent-plasma-as-covid-19-treatment-11612537239

[This article is copied verbatim from the Wall Street Journal with annotations so as to translate what is meaningfully being said by those interviewed!].

The Food and Drug Administration is scaling back its authorization of the use of convalescent blood-plasma for Covid-19 patients in an effort to guide physicians who have faced a confusing thicket of data about the therapy's effectiveness.

The agency said late Thursday that the authorization, a <u>subject of controversy since it was</u> first issued last August, would be revised to limit the use of plasma to <u>hospitalized</u> patients <u>early in the course of the disease</u> and <u>hospitalized patients with a medical condition that impairs their ability to make antibodies.</u> Patients will be allowed to receive <u>only plasma containing high concentrations of antibodies</u>.

"The update is meant so convalescent plasma can best be used on those who will benefit," said Peter Marks, director of the FDA's Center for Biologics Evaluation and Research. "It is being used somewhat more indiscriminately." [High-titer COVID-19 Convalescent Plasma should be given to everyone becoming COVID-19 positive within <72 hours. – NOT just those hospitalized.—C. Andrus]

Dr. Claudia Cohn, chief medical officer of AABB, an organization representing the transfusion-medicine community, said the group plans to issue interim recommendations on convalescent plasma later this month. "There are so many studies coming out with different conclusions," she said. "It is not clean, it is not black and white."

Dr. Marks said the FDA reached its decision after evaluating results from several recent studies. Some showed benefits from convalescent plasma, the antibody-containing fluid derived from the blood of people who have recovered from Covid-19. Others showed no benefit.

Two clinical trials of convalescent plasma for hospitalized patients shut down last month after investigators said there appeared to be no benefit. Three trials involving hospitalized patients recently reported some benefit for the plasma, but only when given to patients soon after admission. Still another trial showed that elderly outpatients given plasma shortly after showing symptoms were less likely to develop serious disease. ---[This was the January 6, 2021 publication in The New England Journal of Medicine which is the ONLY Prospective randomized, placebo controlled trial of CCP administration in one cohesive age group (~70 years of age). THIS IS A LANDMARK STUDY! – C. Andrus]

Arturo Casadevall, chair of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health, called the FDA decision "a step forward." He said, "Physicians in the U.S. for the first time are going to have guidance on when to use it and how to use" convalescent plasma.

Dr. Casadevall is a co-founder of the Covid-19 Convalescent Plasma Project, which helped <u>organize a nationwide expanded-access study of convalescent plasma</u> that began last April.

Despite the contradictory findings, convalescent plasma remains in demand—in part because there are few effective treatments for Covid-19 and many people remain unvaccinated. Since the FDA issued the emergency authorization last August, the blood industry has distributed on average about 20,600 units of convalescent plasma a week to hospitals around the country, according to the American Red Cross.

The FDA's earlier decision to authorize <u>convalescent plasma for hospitalized Covid-19 patients</u> was based in large part on results from an agency-sponsored <u>expanded-access program</u>, through which more than 72,000 patients received plasma. For a study published last month in the New England Journal of Medicine, researchers analyzed data from 3,000 of those patients and reported an apparent survival benefit among hospitalized patients not on mechanical ventilation who received plasma containing high concentrations of antibodies.

But many scientists expressed skepticism about that finding, saying expanded-access studies lack the scientific rigor of traditional trials because they have no control group to compare any apparent effect.

The FDA's Dr. Marks said the authorization of convalescent plasma "could have been handled much better. It had to do with the sense of urgency everyone is feeling. I can't blame anyone for feeling a sense of urgency." -- [As Dr. Marks is the Director of the FDA's CBER (Center for Biologics Evaluation and Research), it was his sole responsibility to have handled it better from March 2020 to the present for the biologic: COVID-19 Convalescent Plasma which is a biosimilar biologic to rabies vaccine, gamma globulin, RhoGam, hypertet, small pox convalescent plasma, IVIG, FFP, etc., etc., etc.]

Dr. Marks also said the data could be confusing. Each unit of convalescent plasma is unique, reflecting the immune response of the recovered patient who donated it. It took time to figure out the best way to measure the antibodies in a unit, he added.

The U.S. isn't the only government trying to establish reliable guidelines on the use of convalescent plasma. In Argentina, a study in elderly outpatients published last month in the New England Journal of Medicine contributed to current recommendations there to treat elderly Covid-19 patients early in the course of their illness. "Plasma supplies are not endless, and invariably public health officials face difficult decisions," said study coauthor Dr. Fernando Polack of Fundación Infant in Buenos Aires. "In any of these decisions, guidelines based on data are necessary and are the best way for clinicians to feel comfortable when facing individual cases."

Louis M. Katz, chief medical officer of Mississippi Valley Regional Blood Center in Davenport, Iowa, which provides blood products for over 120 hospitals, said the evidence supporting the use of convalescent plasma in hospitalized patients is weak. "I think the data is there that it works early," he said. "As you move into sicker and sicker people, the evidence gets thinner and thinner."

In an editorial that accompanied the New England Journal of Medicine paper on the U.S. expanded-access study, **Dr. Katz said convalescent plasma should be used only in patients early in the course of the disease**. The problem with that suggestion, he later added, is the FDA emergency-use authorization still covers only hospitalized patients, who tend to show up at the hospital when they have been sick for a longer

time. – [This is the problem, to become hospitalized, most patients have to be very sick and thus outside the <72 hour window! – C. Andrus, M.D.]

Treating Covid-19 patients who are just starting to show symptoms poses its own challenges. "Logistically, it is very difficult to treat patients earlier," Dr. Katz said. "It's hard to transfuse lots of plasma in outpatients." [BUT IT CAN BE DOWN IN INFUSION CENTERS or Hospital outpatient centers as is done for all infusion chemotherapies, chronic blood transfusions, etc! – C. Andrus. M.D.]

Dr. Marks said a large National Institutes of Health study is now under way to test

convalescent plasma in people with Covid-19 who are sick enough to come to the emergency room but aren't admitted to the hospital, as are other randomized controlled trials of plasma in outpatients. "Until we have those data, we are going to keep the authorization to hospitalized patients," he said. "We will refine it again if appropriate. This is a scarce resource." [High-titer COVID-19 Convalescent Plasma should NOT be a scarce resource as it can be obtained twice a week from the same convalescent donor by PLASMAPHORESIS and the product from each donation will yield 2 doses (4 doses per week) and it can be stored as FFP (Fresh Frozen Plasma) for at least a year! In short, there are over 5,000 blood banks in the US so if each Blood

Bank processed 20 units a day of COVID-19 Convalescent

20 donations / day times 7 days/week times >5000 U.S. Blood Banks times 2 doses of CCP / donation = greater than 1.4 million doses per week of CCP - C. Andrus, M.D.]

Write to Amy Dockser Marcus at amy.marcus@wsj.com Copyright ©2021 Dow Jones & Company, Inc. All Rights Reserved. 87990cbe856818d5eddac44c7b1cdeb8

Appeared in the February 6, 2021, print edition as 'FDA Limits Plasma as Treatment.'

Plasma, that would be:

2021-02-10 Andrus C: Use of COVID-19 convalescent plasma EARLY in the course of the disease. ResearchGate. (Ref 756). https://www.researchgate.net/post/Use_of_COVID-19 Convalescent Plasma EARLY in the course of the disease

2021-02-18 Katz LM: (A Little) Clarity on convalescent plasma for Covid-19. Initially published on January 13, 2021) This editorial was republished in the N Engl J Med, 2021 Feb 18; 384 (7): 666 – 668.

https://www.nejm.org/doi/full/10.1056/NEJMe2035678 In the article, it was not disclosed that Dr. Katz is the Chief Medical Director, ImpactLife: https://www.bloodcenter.org/about/news/authors/dr-louis-katz-a4/ (Ref 770)

[Please note that Dr. Katz was not fully identified by this paper. Dr. Katz is "...the former Chief Medical Officer at America's Blood Centers in Washington, DC, an ABC past president, former board member and a past chair of its Scientific, Medical and Technical Committee. His transfusion medicine career has been dominated by attention to transfusion transmitted infections. He has served multiple terms as the chair of the AABB Transfusion Transmitted Diseases committee and served on many AABB committee and working groups. Dr. Katz is on the Editorial Board of the journal Transfusion, has served on the FDA Blood Products Advisory Committee as a member, industry representative and chair, and is a current member of the HHS Advisory Committee on Blood and Tissue Safety and Availability." — Winn KI, Katz L, Goel R: Dr. Louis Katz, Acting Chief Medical Director. ImpactLife (formerly Mississippi Valley Regional Blood Center). https://www.bloodcenter.org/about/news/authors/dr-louis-katz-a4/

The text of this article that follows is verbatim because it explains the mindset of those involved in the FDA's, NIH's, and The White House's convoluted obfuscation in the lack of treatment during the viremic phase of those infected with COVID-19 with passive immunization (Covid-19 Convalescent Plasma [CCP]) AND THE COVER-UP by US Medicine and the US Government THAT HAS BEEN PERVASIVE OVER THE LAST <u>15 months.</u> While advocating for the appropriate administration early in the viremic phase of Covid-19 (<72 hours from symptoms/diagnosis) in the outpatient setting and NOT IN THE HOSPITAL SETTING, this New England Journal of Medicine editorial fails strongly to emphasis the definitive utility of PASSIVE IMMUNIZATION and thus has been ignored by the medical community, the US federal government, and the US public-at-large. Even after the FDA quietly removed from all its official documentation on 9/2/2020 mandating the strict erroneous CCP administration critera initiated by the FDA / vis-à-vis The White House on March 24, 2020 for use only in severely affected patients--late in the disease--administration of CCP (during the cytokine cascade and bradykinin phase which both are dominant in severely hospitalized patients and then only somewhat effective treatment is supportive) continued. The wrong-time administration of CCP became the de facto standard-ofcare. The majority of 722,000 doses of CCP given over the last 15 months to individuals late in their disease course throughout the U.S.A. (and much of the World) was given at the WRONG TIME. -

And the FDA, the NIH, the VA, *The White House*, the *New England Journal of Medicine*, etc. <u>knew it!</u>

PASSIVE IMMUNOTHERAPY has been used since the late 19th century, and in 1901, the first Nobel Prize in Physiology or Medicine was awarded for serum therapy for patients with diphtheria. During the 1918 pandemic, serum from convalescent patients was used to treat influenza, with some apparent success. 1 Today, the use of immunoglobulins has been established for the prophylaxis and treatment of a variety of infections, including those with respiratory syncytial virus, cytomegalovirus, and hepatitis B or hepatitis A virus. More recently, passive immunotherapy has been evaluated for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and Ebola virus disease. Intravenous human immunoglobulin has revolutionized the management of immunoglobulin deficiency states.

The use of convalescent plasma against SARS coronavirus 2 (SARS-CoV-2) is advocated for the treatment of patients with coronavirus disease 2019 (Covid-19). The experience with influenza A is relevant, and a meta-analysis suggested that **early treatment, before**

critical illness develops, may be an important predictor of the efficacy of passive immunotherapy for that pathogen. 1 The authors of that meta-analysis acknowledged the low quality of the available evidence regarding early treatment. Another meta-analysis of studies of convalescent plasma and hyperimmune immunoglobulin in patients with influenza A and SARS suggested a mortality benefit "when convalescent plasma is administered early after symptom onset." 2 However, in a randomized, controlled trial, high-titer convalescent plasma from patients who had recovered from H1N1 influenza was ineffective against severe influenza A infection in hospitalized children and adults. 3

Initial randomized trials of convalescent plasma in patients with Covid-19 focused on hospitalized patients who were already moderately to severely ill, and these trials provided weak evidence of clinical efficacy. ⁴⁻⁶ Some were underpowered when nonpharmaceutical interventions such as masking and social and physical distancing reduced the incidence of Covid-19 and enrollment was limited. Also, these trials were heterogeneous with respect to the characteristics of the convalescent plasma used (e.g., its antibody content and the stratification of the recipients according to their serologic status). No unexpected safety signals beyond the recognized risks of plasma transfusion (i.e., fluid overload, transfusion-associated acute lung injury, and allergy) have emerged, nor has there been evidence of antibody-dependent enhancement of Covid-19 severity. Accordingly, it is difficult to make actionable conclusions about the clinical value of convalescent plasma.

Observational studies have been more positive than randomized trials; some, but not all, of these studies have suggested modest clinical effects and measurable surrogate virologic outcomes.^{7,8} They have confirmed the safety profile of plasma transfusions but have some of the same issues as randomized trials, in addition to the potential biases and shortcomings inherent in observational studies.

The Food and Drug Administration (FDA) argued that a "totality of the evidence" suggested that the benefits of convalescent plasma would outweigh its risks, and given the lack of effective treatments, the FDA granted an Emergency Use Authorization (EUA) and provided guidance on the manufacture and use of convalescent plasma in hospitalized patients with signs of progressive infection. By contrast, a National Institutes of Health guidelines panel stated that "the data are insufficient to recommend for or against" the use of convalescent plasma. The Infectious Diseases Society of America and the AABB (formerly known as the American Association of Blood Banks) recommend that the use of convalescent plasma be limited to clinical trials, that critically ill patients and those in the intensive care unit (ICU) are unlikely to benefit from transfusions of convalescent plasma, and that convalescent plasma should be used as early as possible in the course of infection (preferably within 3 days after diagnosis) in order to achieve the best outcomes.9

Considering the number of SARS-CoV-2 infections, the paucity of treatment options, and the enthusiasm for and controversy about convalescent plasma, a high-quality, multicenter, randomized, controlled trial is most welcome. Libster and colleagues now report in the *Journal*¹⁰ the results of a well-executed trial of early convalescent plasma in older adult patients in whom symptomatic SARS-CoV-2 infection was diagnosed with the use of a polymerase-chain-reaction assay. In this double-blind trial, 250 ml of convalescent plasma with an IgG titer greater than 1:1000 against SARS-CoV-2 spike (S) protein was compared with saline placebo in patients who were 65 to 74 years of age and had prespecified coexisting conditions and in patients who were 75 years of age or older with or without coexisting conditions.

The patients received convalescent plasma or placebo less than 72 hours after symptom onset. In the intention-to-treat population, a primary end-point event (progression to

predefined severe disease during follow-up) occurred in 16% (13 of 80 patients) and 31% (25 of 80 patients) of the well-matched convalescent plasma and placebo groups, respectively. A dose-dependent effect relative to the antibody titers after infusion was observed, and this effect was larger after the exclusion of 6 patients who had a primary end-point event before infusion. The benefits of convalescent plasma with respect to the secondary end points were consistent with those associated with the primary end point. No serious adverse events were observed. The authors conclude that "early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19." Even before the current trial, the EUA emphasized the potential advantages of early therapy with high-titer **convalescent plasma.** Unfortunately, a direct comparison of antibody levels in the current trial with assays specified in the FDA EUA is not available. Antibody titers in the recipients at enrollment were not provided, so no comment can be made about the usefulness of seroreactivity in patients as a criterion for convalescent plasma use. At this time, convalescent plasma should be reserved for patients in whom the duration, severity, and risk of progression of illness are similar to those in the patients in this trial. Younger high-risk patients (and certain immunodeficient patients) with these disease characteristics should be considered as well.

The supply of convalescent plasma has been tenuous during the marked increase in Covid-19 cases during the fall in the United States, although recent collections have improved. From September 28 through December 27, 2020, distributions of new and stockpiled units of convalescent plasma to hospitals in the United States exceeded collections by 7785 units (Block W: personal communication). If collections are restricted to the high-antibody titers and patient indications described in the article by Libster et al., the supply of convalescent plasma will be stressed. At my center, high-titer collections (as defined by the FDA) account for only 19.5% of seroreactive convalescent plasma donations. Shifting the pool of potential recipients away from those included in the EUA to the many infected outpatients whose risk of hospitalization and eventual need for advanced care cannot be precisely estimated should lead to the extension of convalescent plasma transfusions to prehospital venues (although this is not yet permitted in the EUA).

<u>Uncontrolled compassionate use of convalescent plasma in patients other than those</u> <u>with an early infection that is likely to progress to more severe illness should be</u> <u>discouraged</u>, even though clinicians recognize how difficult it can be to "just stand there" at the bedside of a patient in the ICU. Constraints on therapies for Covid-19 that are effective for limited patient populations are a powerful argument for continued consistent adherence to recommended nonpharmaceutical interventions and the rapid deployment and uptake of effective vaccines.

In an obfuscating way, Dr. Katz confirms that when high-dose COVID-19 Convalescent Plasma is given **EARLY**(<72 from time of onset or diagnosis) and is compared with placebo in age-matched patients ~70 years of age, progression to severe COVID-19 disease (e.g. pneumonitis, blood clots, etc.) is 16% versus 31%, respectively.

THUS, COVID-19 CONVALESCENT PLASMA when given <u>EARLY to an AGE COHESIVE GROUP</u> in the VIREMIC PHASE OF COVID-19 (<72 HOURS) has a 50% DECREASED / OBSERVED REDUCTION IN PROGRESSION to the LATER MULTIORGAN-SYSTEM PHASE OF COVID-19 INVOLVING (1) THE CYTOKINE CASCADE STORM and (2) the ACCUMULATION OF DETRIMENTAL LEVELS OF BRADYKININ.

2021-02-18 Whyte J: FDA revises EUA for COVID-19 Convalescent Plasma. WebMD. John Whyte, M.D., Chief Medical Officer at WebMD interviews Peter Marks, M.D., PhD, Director for the Center for Biologics Evaluation and Research at the U.S. FDA: FDA revises EUA for COVID-19 convalescent plasma. https://www.webmd.com/coronavirus-in-context/video/peter-marks-plasma (Ref 771)

The following is a very important interview as Peter Marks, M.D., PhD as the Director for CBER at the FDA had the ability in March 2020 to have designated COVID-19 Convalescent Plasma a Biosimilar Biologic (like rabies vaccine, HyperTet, RhoGam, IVIG, etc.) and the designation of "Investigational" and all the Expanded Access / (compassionate use only) would have been avoided. This would have precluded the issuing of the eligibility criteria of March 24, 2020 which directed administration late in the course of the disease—THE WRONG TIME as is confirmed by Dr. Marks in the 2/18/2021 interview! Immediately following is from the March 24, 2021 FDA announcement. https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20 %20FDA.pdf

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

- · Eligible patients for use under expanded access provisions:
 - o Must have laboratory confirmed COVID-19
 - Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dvspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - · Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale...

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

- multiple organ dysfunction or failure
- · Must provide informed consent

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease

0.1 2022-09-11 Dear Mr. President Case Report EDIT 9-22-2022

This submission is NOT for financial gain but for educational purposes only for ALL the American people

Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Start of the interview of Dr. Marks by Dr. Whyte:

JOHN WHYTE: Welcome, everyone. You're watching "Coronavirus in Context." I'm Dr. John Whyte, chief medical officer at WebMD. We're spending a lot of time talking about vaccines. But we can't forget about the role of therapeutics for those persons who have caught COVID and are having a serious case. And there's been some recent changes in when and how we should use convalescent plasma.

So to help explain these changes, I've asked Dr. Peter Marks. He's the director for the Center for Biologics Evaluation and Research at the US Food and Drug Administration. Welcome back, Dr. Marks.

PETER MARKS: Thanks very much for having me.

JOHN WHYTE: Let's just take a minute and remind our audience-- we have a lot of folks from Medscape, but also consumers-- what is convalescent plasma?

PETER MARKS: So convalescent plasma is the blood plasma that's taken from an individual who has been infected with COVID-19 and who's recovered from the infection. In some cases, they might not even have known they had the infection, but they obviously did. And they might have antibodies that have been detected and told they had COVID-19, or they might have had a PCR test when they were sick with COVID, were told they had COVID-19, and afterwards, after they recover and they're fully recovered, they're eligible to potentially donate convalescent plasma, which is usually taken by plasmapheresis. People are put on a machine for about an hour, and the blood products taken out. And the blood cells are given back to the person. The plasma is taken off.

JOHN WHYTE: Now, the FDA authorized the use, under an emergency use authorization, of convalescent plasma in August of last year. And recently, you revised that authorization-- actually, in many ways made it more restrictive. Let's go over what the change in the EUA is.

PETER MARKS: Right. So the emergency use authorization that was issued in August was a very broad emergency use authorization, because at that time we were relying on the evidence at the time which said that it appeared that convalescent plasma could potentially benefit a broad swath of people. And we weren't really sure who it might benefit the absolute most. We knew it was best when given in high titer, and we knew that it seemed to be best in people who were treated earlier. But we couldn't rule out that it was having some benefit to people later on in the course of disease.

JOHN WHYTE: And at that time, they didn't have to be hospitalized.

PETER MARKS: We always required that the patients be hospitalized. It was always hospitalized patients. And what happened, then, is over the course of the past few months-- we follow the literature very closely-- there have been studies that have come out of various places. Some have been negative for convalescent plasma-- they said that it's not had a beneficial effect. Others have been quite positive.

And over the course of time, we've looked closely at them, and we sorted them out. And it became pretty clear that when people were treated early on with high-titer convalescent plasma, they seemed to be showing some benefit. And when you treat late, you just don't see that benefit. Particularly when you treat people who have been on a ventilator, it just—with the rare exception of people who have defects in immunity, people who have diseases like hematologic malignancies like chronic lymphocytic leukemia—those people, they may benefit late on, because they don't make antibodies.

But for the large majority of people who have normal immune systems, if you treat late, convalescent plasma is not seeming to benefit, whereas if you treat early, within the first few days after diagnosis, the data are increasingly supporting that there is some benefit there. It's not a massive benefit. It's a modest benefit.

JOHN WHYTE: How would you articulate that benefit?

PETER MARKS: I can cite the data that we have from roughly 20,000 individuals who received 1 unit of convalescent plasma. Roughly half of those people got high titer and half of them got low titer of various levels. And the people who got the higher-titer plasma had about a 2-percent absolute reduction in mortality at seven days, which translates into about a 15-percent relative reduction if they were not intubated.

If they were intubated, they were on a ventilator, then there really wasn't any benefit. So those data really helped push us along towards saying it was time to kind of narrow down the emergency use authorization to say, look, don't use this late in people who are intubated—that is, on a ventilator. Use it early on or earlier on in the course of disease.

Now, your next question might be, why not just use it as an outpatient? Hum. And the answer is--

JOHN WHYTE: Now you're interviewing yourself.

PETER MARKS: Nah. I might as well do that. I've done this enough. But the reason why we're not there yet is because we're waiting for some very well-designed studies that are being conducted, one by the National Heart, Lung, and Blood Institute, which will give us a good answer about the potential benefit in that setting.

JOHN WHYTE: Well, that's why I was asking you about hospitalized patients. Because if we talk about-- you mentioned it has to be used early on in the disease-- but what about severity of disease? Because many patients that aren't coming to the hospital until they're much further along-- so how do you do it, in the sense you want to do it early on, within those first couple of days, but sometimes we're telling patients not to come to the hospital or to the ER. So how do we balance that? So what's the severity of disease?

PETER MARKS: I think right now the way we balance it is we say that if you're somebody who's got early disease and you're interested, get onto the www.ClinicalTrials.gov and find one of the sites around you that might be doing outpatient clinical trials with convalescent plasma. There are a number of sites doing that.

But I think, otherwise, when people are admitted to the hospital, it's probably a good thing for physicians to think right away, is this somebody for whom convalescent plasma may make sense? Again, if someone's intubated in that first couple days, maybe not. On the other hand, if someone needs supplemental oxygen, those patients did seem to benefit.

JOHN WHYTE: Now, let's talk about the person's underlying immune response, their humoral immunity. So who are those patients? Many patients are often asking about, what if they're immunocompromised? What do they qualify for? Talk to our listeners about what's that patient population—because that's a component, their underlying immunity function.

PETER MARKS: So it's a great question. And we've actually kept up with the case reports that have been coming out. They're not trials, but they're a case series that have come out from around the globe, and it's very convergent. If you treat people who don't make a sufficient amount of antibody, either because they have a primary immunodeficiency syndrome or because they have [INAUDIBLE] cancer, and they can't make them, if you treat them, even if you seem to treat those people late, they seem to have benefit.

And there are some amazing case reports—obviously, it's always N-of-1—case reports, you always have to take with a grain of salt—but where people even very late on have had very good responses clearing viremia. So that kind of makes sense, right? Because if you're not able—what we think, at least, that the antibodies are doing here—the antibodies in convalescent plasma are acting like an antiviral, right? And if you give it early, they're acting like an antiviral would early on in getting things under control. Later on in the course of disease, where there are other organ damage effects, that's not the best time for an antiviral. And for those who are immunocompromised, it may be that they just have ongoing viremia, and you need to clear it. And giving them convalescent plasma helps take care of that.

JOHN WHYTE: One question we have gotten asked, Dr. Marks, is for those patients who have been fully immunized, are they able to donate plasma?

PETER MARKS: So it's a great question. And it's one we're still debating. Right now, if people have not had COVID-19 and get immunized-- so they're people who are COVID-19-negative to start, then get immunized-- we're not considering them as convalescent plasma donors, because they're making antibodies against just the S protein that are in the current generation of mRNA vaccines that are authorized.

We don't know, in terms of the convalescent plasma response that we're seeing, how much of the benefit is from the S-protein antibodies versus N-protein antibodies or other antibodies that are there. And until we have a little better idea on that, we're a little hesitant to swing over to have vaccinated individuals donate.

But this is an absolutely great question, because we're very much looking into this

now. It would be nice to understand, because soon we're going to have a large population of people who will be fully vaccinated, probably with high titers of S antibodies, and it would be nice to know this. So stay tuned. We do that for other infectious diseases, and maybe we'll see it coming for COVID-19 soon enough.

JOHN WHYTE: Tell us how staff are doing. You had your general work that you had to do, in terms of vaccines, other biologics. Now you have the whole issue of COVID. How is everyone managing it?

PETER MARKS: Well, I have to say, we are incredibly lucky at FDA. We have a staff that has risen to the occasion in an amazing way. They're keeping the normal freight moving. And while they're keeping the normal freight moving, they are taking care of the avalanche of COVID-19-related applications.

Now, in some areas, there are a little lower number of applications than in others. But if you look, for instance, in the vaccine area, there is an avalanche there. And they're doing an incredible job keeping up. Same thing with, actually, some of the cellular therapies that have come in, and even the antibody therapies, et cetera. There are lots of them, right?

Our folks have done just an incredible job pitching in. People who have a little less work pitch in to those who are almost getting underwater in work. So it's been really wonderful. It has taken its toll. People are getting a little tired. And we're trying to make sure that we take care of people. But we're very lucky that people have really had such commitment to public health.

JOHN WHYTE: Absolutely. And then finally, all these emergency use authorizations that are happening across the agency-- do you expect sponsors to apply for full licensure in a few months?

PETER MARKS: Yeah. So I— for the vaccine sponsors in particular, we've told them that if they want to come in for an EUA, they should expect— it's actually in our guidance— they should expect that they're going to come in for a biologics license application. And so that's why the work isn't going to end soon, because as we're now dealing with some of the emergency use authorizations where the vaccines are becoming more mature, they've been in use for a little bit, I would suspect in the not-too-distant future we may see their biologics license applications. And so there will be kind of a cohort that will come along of license applications in the coming months.

JOHN WHYTE: Well, Dr. Marks, I want to thank you for taking the time, the work that you and all the staff at the Center for Biologics Evaluation and Research and all of FDA are doing to keep us all safe.

PETER MARKS: Thanks so much for having me today.

JOHN WHYTE: And if you have any questions about COVID, drop me a line. You can email us at drjohn@webmd.net as well as post it on Facebook, Twitter, and Instagram. Thanks for watching.

2021-03-02 NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms – Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health

announcement is: (Ref 785). https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms

The actual clinic trial, *Convalescent Plasma in Outpatients with COVID-19 (SIREN C3PO)* NCT04355767, was:

https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767 &draw=2&rank=1

There are no reported results on the Clinical Trials website of which the NIH is making its decision to halt the trial. The trial was underpowered where there was no stratification by age and the study was discontinued with recruitment of only half the number of planned patients. This study was run by: **SIREN**, **S**trategies to **I**nnovate eme**R**g**EN**cy Care Clinical Trials, https://clic-ctsa.org/node/9426.

NIH Announcement to discontinue the trial on March 2, 2021:

Launched in August 2020, the Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO(link is external)) was being conducted at 47 hospital emergency departments across the United States and had enrolled 511 of the 900 participant recruitment goal. It was specifically looking at the effectiveness of COVID-19 convalescent plasma – blood plasma derived from patients who have recovered from COVID-19 – in adults who came to an emergency department with mild to moderate symptoms they had for a week or less. These patients also had at least one risk factor associated with severe COVID-19, such as obesity, hypertension, diabetes, heart disease, or chronic lung disease, but none were ill enough at the time to be hospitalized.

(<u>C3PO</u>(link is external) <u>https://siren.network/clinical-trials/c3po</u>

C3PO Clinical Trial of COVID-19 Convalescent Plasma of Outpatients

Registered with ClinicalTrials.gov: NCT04355767

https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1

This is a registered NIH ClinicalTrials.gov Award Number: 10T2HL156812-01

Status: No new randomizations as of February 25, 2021.

NIH Press Release (March 2, 2021)

Media inquiries: Refer to <u>Lenora Johnson</u>, <u>DrPH</u>, <u>MPH</u> and <u>Mark</u>
 Sampson, and to this press release.

The Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO) is a multi-center randomized, single blind, two arm, placebo controlled phase III trial with blinded outcome assessment to establish the safety and efficacy of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.

COVID-19 is a respiratory illness caused by the *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). As of May 1, 2020, over 3 million persons worldwide have been diagnosed with COVID-19 and approximately 250,000 persons have died from this disease. The majority (80%) of cases are categorized as mild, while approximately 15-20% of cases are categorized as severe, with about 5% of all cases progressing into critical illness, characterized by hypoxemic respiratory failure, shock, and end-organ failure. Among the 5% who develop severe disease, as many as 50% die. At present there is no specific therapy for preventing the progression of COVID-19 from mild to severe disease.

Passive antibody therapy using plasma from donors who have been infected and then recovered (convalescent plasma, CP) contains neutralizing antibodies against the infectious agent. Specifically, CP has been used in different respiratory illness epidemics, including the 1918 influenza pandemic, the 2003 SARS-CoV-1 outbreak, and the 2009 H1N1 influenza pandemic. Use of CP for emerging infections has persisted because of strong mechanistic and observational data, but efficacy has yet to be well tested or demonstrated in clinical trials. At this moment, there is no high quality evidence to support the efficacy of CP for treating COVID-19 illness. Conceptually, CP has the highest chance of showing efficacy if used for early treatment of patients at the highest risk for severe disease and mortality.

The overarching goal of this trial is to confirm or refute the role of passive immunization as a safe and efficacious therapy in preventing the progression from mild to severe/critical COVID-19 illness and to understand the immunologic kinetics of anti-SARS-CoV-2 antibodies after passive immunization.

For more information on C3PO and convalescent plasma go to our <u>In the News</u> page. (https://siren.network/clinical-trials/c3po/in-the-news)

C3PO IN THE NEWS

March 10, 2021

 Convalescent Plasma Strikes Out As COVID-19 Treatment https://www.npr.org/975365309

October 22, 2020

 OHSU reserchers say they're having trouble recruiting patients for COVID-19 convalescent plasma trial

https://www.kptv.com/ohsu-researchers-say-theyre-having-trouble-recruiting-patients-for-covid-19-convalescent-plasma-trial/video_767f3558-10aa-5201-ad47-94322b60070d.html?block_id=988363

September 8, 2020

 NIH clinical trial explores use of convalescent plasma in at-risk outpatients with early COVID-19

https://www.nhlbi.nih.gov/news/2020/nih-clinical-trial-explores-use-convalescent-plasma-risk-outpatients-early-covid-19

August 25, 2020

 UF Health enrolls first patients in national COVID-19 study on convalescent blood plasma

 $\frac{https://m.ufhealth.org/news/2020/uf-health-enrolls-first-patients-national-covid-19-study-convalescent-blood-plasma}{covid-19-study-convalescent-blood-plasma}$

August 19, 2020

New clinical trial at OHSU tests donated antibodies
 https://news.ohsu.edu/2020/08/18/new-clinical-trial-at-ohsu-tests-donated-antibodies

August 6, 2020

Will COVID-19 finally provide an answer on convalescent plasma?
 https://www.medpagetoday.com/infectiousdisease/covid19/87936

August 3, 2020

 UM and Other Michigan hospitals to treat COVID-19 patients with convalescent plasm.

https://www.michiganradio.org/post/um-and-other-michigan-hospitals-treat-covid-19-patients-convalescent-plasma

July 30, 2020

 Michigan hospitals test if plasma from recovering patients can curb COVID-19

https://www.bridgemi.com/michigan-health-watch/michigan-hospitals-test-if-plasma-recovering-patients-can-curb-covid-19

- Researchers at the University of Michigan's Michigan Medicine and three other medical centers were awarded a total of \$7 million from the National Heart, Lung, and Blood Institute (NHBLI) to study convalescent plasma in reducing symptoms of COVID-19 in patients with mild cases, Michigan Medicine announced Thursday.
 - https://www.clickondetroit.com/video/health/2020/07/30/michigan-medicine-7-million-in-funding-for-covid-19-therapy-trial/
- Michigan Medicine and three other medical centers receive \$7 million COVID-19 outpatient convalescent plasma therapy trial https://www.uofmhealth.org/news/archive/202007/michigan-medicine-and-three-other-medical-centers-receive-
 - 7?fbclid=IwAR2Rr1QbiOj6OxC0dcbv2Hw0Cn6uMlnx0BTz-buGJCf4SozAqutNDa6 1qo
- Trump urges people who who have recovered from COVID-19 to donate blood plasma
 - https://www.washingtonpost.com/health/2020/07/30/trump-urges-people-who-have-recovered-covid-19-donate-plasma/
 - $\frac{https://www.c-span.org/video/?474383-1/president-trump-roundtable-discussion-donating-plasma}{discussion-donating-plasma}$

July 29, 2020

- UPMC studying whether convalescent plasma help coronavirus patients with mild symptoms
 - https://pittsburgh.cbslocal.com/2020/07/29/coronavirus-study-convalescent-plasma/
- COVID-19 trial to study convalescent plasma in outpatient setting https://web.musc.edu/about/news-center/2020/07/29/covid19-trial-to-study-convalescent-plasma-in-outpatient-setting

March 10, 2021

 Convalescent Plasma Strikes Out As COVID-19 Treatment https://www.npr.org/975365309

2021-03-10 Harris R: Convalescent plasma strikes out as COVID-19 Treatment. NPR, March 10, 2021, 5:01 AM ET

More than half a million Americans have received an experimental treatment for COVID-19 called convalescent plasma. But a year into the pandemic, it's not clear who, if anyone, benefits from it.

That uncertainty highlights the challenges scientists have faced in their attempts to evaluate COVID-19 drugs.

On paper, treatment with convalescent plasma makes good sense. The idea is to take blood plasma from people who have recovered from COVID-19 and infuse it into patients with active infections. The antibodies in the donated plasma, in theory, would help fight the virus.

Based on that idea, last March Dr. Nicole Bouvier at the Icahn School of Medicine at Mount Sinai Hospital in New York decided to give it a try.

She recalls thinking, "we have this new disease that didn't have any known therapies, and convalescent plasma has been used in new epidemic and pandemic diseases," as recently as in an Ebola outbreak in West Africa a few years ago.

She says she was the first doctor to get special permission from the Food and Drug Administration to use it as an experimental treatment.

It was a huge commitment to line up people willing to donate plasma as well as to treat patients themselves, "so it was a big production," she says. "We ultimately screened over 70,000 people" and identified around 20,000 who had high antibody levels in their blood plasma.

Mount Sinai treated more than 1,400 patients, including throughout the height of New York City's nightmarish COVID-19 outbreak last spring. But all the while Bouvier had no idea whether the plasma really worked.

Finally, a couple of weeks ago, she had seen enough data from carefully controlled studies — and decided to stop offering the treatment.

"The straw that broke the camel's back was two very large cohort trials," she says. The RECOVERY Trial in the United Kingdom had studied more than 10,000 volunteers and found no benefit. Another one called CONCOR-1, run by Canadians, had studied nearly 1,000 patients. It, too, stopped recruiting new patients because doing so would have been futile.

But those studies focused on people sick enough to be in the hospital. Dr. Arturo Casadevall at the Johns Hopkins Bloomberg School of Public Health is one of the prime advocates for convalescent plasma. He says he thinks the treatment needs to be done sooner, in the outpatient setting.

"From the very beginning here at Hopkins we set out to do outpatient trials," he says. "The trials were set up in March [of 2020], however it took many months to get the money to do it." With taxpayer money nowhere to be found, the study ultimately went forward with funding from the billionaire Michael Bloomberg, Casadevall says.

A year later, the study at Hopkins still doesn't have results. And it's not just a question of funding. The entire U.S. medical research system isn't set up to do what's needed to identify new treatments during a pandemic.

Dr. Derek Angus, chair of critical care medicine at the University of Pittsburgh, says that in a public health emergency scientists should be able to evaluate new treatments at hundreds of hospitals, in a matter of months.

"People might roll their eyes and say that's impossible, but that's largely what the United Kingdom has done," Angus says. "For all our capacity in the United States, it's depressing that we can't do a U.S. version."

The U.K. was able to launch its vast study quickly because Britain has a national health system that not only provides treatment but can conduct research. Research in the U.S. is balkanized among universities, drug companies and funders.

"We pride ourselves on having a very federated, independent system," Angus says. "But, gosh, that is very hard to turn on a dime to solve national problems."

To give just one example, a national network of emergency room physicians got federal funding to treat people with convalescent plasma, in a study named C3PO. Their patients were sick enough to show up in the emergency room, but well enough to go home afterward.

"We should have been able to get this done as quickly as they did in the U.K.," says Dr. Kevin Schulman at Stanford University. "It was just a much slower process to set up."

Schulman at Stanford was responsible for some of the logistics. And they were a nightmare, he says.

"I said tongue in cheek at some point when we had five patients in our study that we had at least 500 people touch a paper for the five patients we had recruited. And that's the opposite in the UK."

"Some of the contracts for the trial we are still negotiating even today," he adds. "You know, the U.K. didn't have any of that."

The C3PO study recently stopped recruiting patients. It had enrolled about 500 out of a planned 900, but an independent monitoring board concluded that continuing would have been futile.

This further casts doubt on the value of convalescent plasma.

"I don't see any point in offering plasma outside a clinical trial," says Angus from Pitt.

Several trials are ongoing. And there's still a chance that some of them could identify a group of patients, treated at a particular time with a particular concentration of plasma, who would benefit. So Bouvier at Mount Sinai hasn't given up on it completely.

In retrospect, it's understandable why convalescent plasma doesn't help people hospitalized with significant illness, she says. Serious illness is caused primarily by the body's reaction. Respiratory viruses like these don't persist for long. "They're sort of like, 'wham, bam, thank you, ma'am.' And then they're gone," Bouvier says.

"If a study comes along that identifies a population in whom convalescent plasma is useful, we will use it in that population" she says.

And if it does appear to be helpful for people who are early in the course of disease, that raises another question: Would plasma be better than the monoclonal antibody drugs already authorized by the Food and Drug Administration for that purpose and easier to use?

Casadevall at Hopkins argues that plasma might be better, especially if new virus variants can evade the antibody drugs. Antibodies in the plasma of people who have recovered have apparently been successful in controlling whatever virus they encountered, so the treatment actually evolves along with the pandemic.

But to figure out whether convalescent plasma is better than monoclonal antibodies could require another large, time-consuming study in a research system not set up to be nimble.

You can contact NPR Science correspondent Richard Harris at rharris@npr.org.

Mr. President, in the article that follows, the NIH, the FDA, and *The New England Journal of Medicine* **published** the "results from the C3PO SIREN trial" NINE MONTHS LATER that the FDA used to withdraw its support of COVID-19 Convalescent Plasma on March

2, 2021 thus avoid scientific scrutiny for nine months. This study is a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published. Personally, I think the NIH, the FDA, and the editors of *The New England Journal of Medicine* should explain themselves to the American Public.

2021-11-18 Korley FK, Durkalski-Mauldin V, Yeatts SD, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswall S, Kaplan A, Lowell E, Mcdyer JF, Quinn J, Triulzi DJ, Van Huysen C, Stevenson VLM, Yadav K, Jones CW, Kea B, Burnett A, Reynolds JC, Greineder CF, Haas NL, Beiser DG, Silbergleit R, Barsa W, Callaway CW, for the SIREN-C3PO Investigators: Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO ClinicalTrials.gov number, NCT04355767.] (Ref 1022).

 $\underline{https://www.nejm.org/doi/pdf/10.1056/NEJMoa 2103784?article Tools = true}$

The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. (Advarra is a propriety company which on their internet listing are: Industry Experts—The Advarra Advantage: Our Expertise:

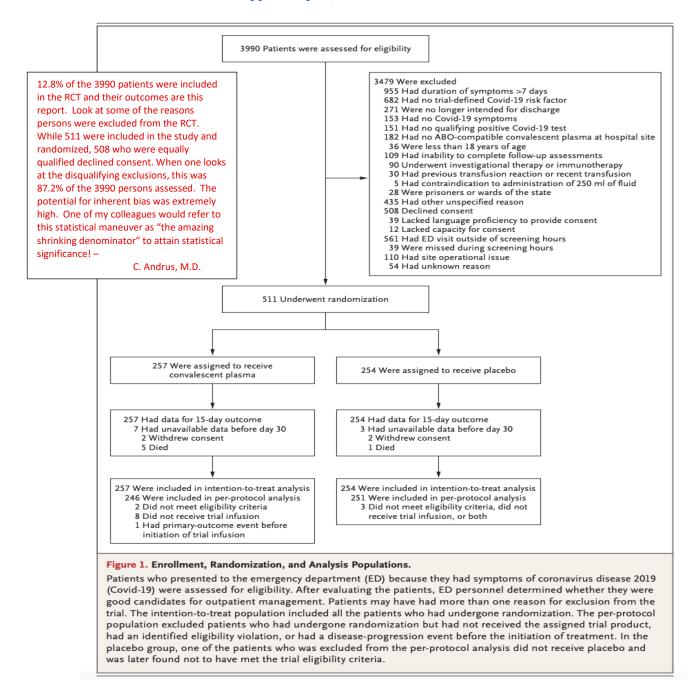
The Advarra advantage is built on our industry and domain expertise. Our experts are change agents and thought leaders with deep experience in clinical research. Together, we solve mission-critical challenges and bring life-changing therapies to participants faster. (Please note, Advarra's experts listed on their website https://www.advarra.com/about/industry-experts/ include **NO MEDICAL CLINICIANS LIKE AN M.D. OR A D.O.** In short, the SIREN-C3PO clinical trial NCT04355767 was reviewed by a proprietary company and **NOT** by any University School of Medicine IRB, any participating Hospital IRB, or the FDA's IRB directly.)

PLEASE note that the complete article and the supplementary appendix can be found at:

Korley FK, Durkalski-Maudin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, et al., for the DIREN-C3PO Investigators*: Early convalescent plasma for high-risk outpatients with Covid-19. URL from article N Engl J Med 2021 Nov 18; 385: 1951-1960.

https://www.nejm.org/doi/10.1056/NEJMoa2103784 This reference from the article is just an abbreviation; The full article is https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=tru e and the Supplementary Appendix which is very important can be found at

(https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nej moa2103784_appendix.pdf).



In Figure 1. **Enrollment, Randomization, and Analysis Populations**, of the 3990 patients presenting to the Emergency Room, 3479 (87.2%) were excluded as listed in the box above. The number of eligible patients that refused to participate in this placebo RCT was 508 and with the 561 that presented outside of ED screening hours and thus were rejected. These two exclusion factors totaled over twice as many patients (1069) as were included in this study of 511. What is more, when the NIH announced the

closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum ß that the researchers agreed upon for a valid study), it proceeded to conclude that early administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is probably a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published.

It should also be noted that at the end of the author list on the front page of this article, it is stated: ...for the SIREN-C3PO Investigators* where the "*" refers to the statement in the right margin:

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org which is 20 pages long (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nej_moa2103784_appendix.pdf) In this Supplementary Appendix major criteria for inclusion in the study changed from Protocol Version 1 of June 17, 2020 through Version 2 of July 2, 2020, Version 3 of September 7, 2020, Version 4 of November 3, 2020 to Version 5, February 16, 2021:

Has at least one study defined risk factor for severe COVID-19 illness:

Age \geq 50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression

Yet, in Table 1. Characteristics of the Patients at Baseline:

Characteristic	Convalescent Plasma	Placebo
	(N=257)	(N=254)
Median age (IOR)	54 (42-62)	54 (40-62)

there were patients of 42-49 years in the Convalescent Plasma group and patients of 40-49 years in the placebo group. Those patients should have been excluded due to their "youngness" that violated the stated inclusion criteria of all five Protocol versions of this trial. Were the SIREN-C3PO investigators, the NIH, and the editors of *The New England Journal of Medicine* being truthful to the American public? Has this paper done a disservice to the American public and to the World? As the NEJM attests to the participation in the *International Committee of Medical Journal Editors (ICMJE)*, they owe the American people an independent (independent from the U.S. Government and *The New England Journal of Medicine*) peer review of this paper with regards to appropriateness: **Simply put, can this paper even conclude that which it concludes?**

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5.0 2021-09-19 Tragedy of Electronic Overwriting.pdf

5.0 2021-09-19: THE TRAGIC METHOLOGY OF ELECTRONIC OVERWRITING OF OFFICIAL GOVERNMENT DOCUMENTS IS AN OBSTRUCTION OF JUSTICE

Dear Mr. President:

Please forgive my forwardness of this cover letter of the documentation I will be presenting to you. Over the last 18 months I have submitted documentation with the U.S. Department of Health and Human Services through the office of the NIAID of the National Institutes of Health, the Office of the Commissioner of the FDA, and many other federal offices including the Office of the President of the United States with little response to my advocacy. As a federal physician of 24 years of service in the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs, it is my duty to bring to your attention that which has collectively been detrimental to the people of the United States of America. While my past focus has been to promote *Passive Immunization* methodologies in the early treatment (<72 hours from diagnosis) of COVID-19 (e.g.: Convalescent Plasma, Convalescent Sera, Monoclonal Antibodies, and Monoclonal Antibody cocktails), the most glaring foundational problem common to our addressing the conoravirus SARS-CoV-2 has been harmful selective transparency, misdirection, **obfuscation**, and lies promoted by U.S. Medicine, U.S. Medical Research, U.S. Pharma, and agencies of the Executive Branch of the Federal Government (e.g.: FDA, NIAID, NIH, CDC, USPHS, VHA of the DVA, etc.). By (1) altering their adherence to their own-stated policies and directives; (2) violating or negating public laws: e.g.: EMTALA, PL-89-97 and The Right to Try Act, PL-115-176; and (3) misinterpreting fundamental immunology concepts; (4) misapplying and ignoring research ethics as proclaimed by the Nuremberg Code, the Helsinki Accords, and the Belmont Report; (5) redefining incorrectly key medical terminology, and (6) misrepresenting the very definitions promoted by the U.S. Department of Health and Human Services: e.g.: Clinical Trials, placebos, EUA, Expanded Access, and the very foundational Congressionally-mandated decrees establishing the FDA (over a century ago), U.S. Medicine and the U.S. Government have synergistically failed the American people!

Attached to this cover letter are multiple aspects of where we, as the U.S.A. in the fight against COVID-19 went wrong. Below is the latest personal example that was presented to my family by my wife purchasing two of the at-home COVID-19 Antigen Self tests: Abbott's BinaxNOW and Quidel's QuickVue. Both contain the following statement (with slight variations):

This product has not been FDA cleared or approved, but has been authorized by the FDA under an Emergency Use Authorization (EUA) for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens...

Except for Remdesivir (VELKURY, NDA #214787, October 22, 2020) and Pfizer's COVID-19 vaccine (COMIRNATY, BL 125742/0, August 23, 2021), all other agents being utilized in the

fight of COVID-19 for testing, treatment, and prevention of COVID-19 are under Emergency Use Authorizations (EUAs) which mean they are <u>all</u> "Investigational" or in Medical Research terminology: **Experimental**. We, as a nation, have given out over 200 million doses of vaccines (**Active Immunization**) under the auspices of **Medical Research experimentation** during this pandemic.—It is no wonder that a large percentage of the American people still refuse to be vaccinated with these "Experimentational Agents." The generic term **Passive Immunization** (Convalescent plasma/sera and monoclonal antibodies) has never been mentioned to the American public even though ~722,000 units of COVID-19 convalescent plasma/sera have been administered over the last 18 months **AT THE WRONG TIME late in the course of the disease!**

Normally, in NIH authorized Clinical Trials and in policies of the FDA, successful completion of a phase 1 trial with regards to <u>safety</u> is met when approximately 20-40 individuals with the disease have had minimal side-effects attributable to the Investigational agent when administered. When efficacy has been demonstrated in Phase 2/3 studies (200-400 individuals) then an agent usually receives FDA approval as a new drug or biologic. Over the last 18 months, hundreds of thousands of these agents of Active and Passive Immunization have been given out by hospitals, infusion centers, and other emergency sites under the auspices of EUAs—Experimental Administrations.

While someone purchasing the OTC tests mentioned above assumes they are <u>screening tests</u> for SARS-CoV-2 antigens in the nares of an individual, **neither meets medical sensitivity significance criteria** for a screening test of 2 standard deviations from the mean (a 95% confidence level): Abbott's BinaxNOW 91.7% sensitivity and Quidel QuickVue At-Home OTC COVID-19 Test of 83.5% sensitivity. **Most of all Mr. President**, while both tests within their packaged directions states that the reagents of the test can be harmful if contacted by an individual, NO WHERE is it stated the legal FDA warning of: KEEP OUT OF REACH OF CHILDREN (21 CFR 369.9) on the packaging. I chose this example because it presents minor lapses of dereliction to duty by the FDA when overall there have been major infractions by the FDA and the NIH.

Throughout the last 18 months, both the FDA and NIH have disregarded or conveniently overlooked the intent, if not the letter-of-the-law, regarding generic adherence and protection of patients' rights (and more specifically, they ignored PL-115-176, The Right to Try Act at every turn) which, in some circumstances, may have been illegal but, in all instances, violated the collective trust of the American people. Collectively, shame on U.S. Medicine and shame on the agencies of the U.S. Department of Health and Human Services! They should all apologize to the U.S. people!

Mr. President: As Dr. Fauci, you, and I grew up in the era of the Roman Catholic Latin Mass, we of U.S. Medicine and the Executive Branch of the U.S. Government should all be beating our breasts and stating: Mea Culpa, Mea Culpa, Mea Maxima Culpa. In the attached documentation, I will try to explain the following:

1. My summarization of the natural course of the disease of COVID-19 caused by the coronavirus SARS-CoV-2 including:

- a. The size of the coronavirus SARS-CoV-2 (50 140 nm) and its implications regarding N95 masks (there are no true antiviral masks and N95 masks inhibit 95% of particles less than 300 nm in size). https://blogs.cdc.gov/niosh-science-blog/2009/10/14/n95/ and https://www.news-medical.net/health/The-Size-of-SARS-CoV-2-Compared-to-Other-Things.aspx
- b. The implications of the longitudinal graphs of daily new cases of COVID-19 and daily deaths attributable to COVID-19. https://ourworldindata.org/coronavirus Mr. President, did you know that the graphs of the decline of new cases and new deaths represent logarithmic decays that approach zero daily cases and deaths asymptotically?
- c. As we have <u>not</u> until this summer officially treated early (before the cytokine cascade and the bradykinin storm late phase) COVID-19 with passive immunization (monoclonal antibodies), one can mathematically define the natural untreated death rate of COVID-19 patients. The derived equations and graphs from the CDC weekly reports regarding mortality by age groups are the following https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge:

0-45 years	y = 0.0008x - 0.0103	$R^2=0.8254$
46 - >85 years	y = 0.0049x - 0.1216	$R^2=0.9972$

From 4/2020 to present:

Age Range	Mortality %	Deaths by Age Group
	Infected	100,000 in that Age Group
0 - 17 yrs	0.05%	50 / 100,000
18 - 29 yrs	0.41%	410 / 100,000
30 - 39 yrs	1.19%	1,190 / 100,000
40 - 49 yrs	3.10%	3,100 / 100,000
50 - 64 yrs	15.47%	15,470 / 100,000
65 - 74 yrs	21.63%	21,630 / 100,000
75 - 84 yrs	27.06%	27,060 / 100,000
\geq 85 yrs	31.09%	31,090 / 100,000

- 2. The chronology of what went wrong in the implementation of Passive Immunization from January 2020 to the present.
- 3. It would be my suggestion along with your present COVID-19 White House Task Force members, you might invite to the White House for an educational informational session for you the following physicians and present and former governmental individuals:
 - Francis S. Collins, M.D.; Anthony Fauci, M.D.; Stephen Hahn, M.D.; Janet Woodcock, M.D., Debroah Birx, M.D.; Peter Marx, M.D.; RADM Denise M. Hinton, RN, MS; Michael Joyner, M.D.; Arturo Casadevall, M.D.; Liise-anne Pirofski, M.D.; Jay Epstein, M.D.; Louis M. Katz, M.D.; Leonard Schleifer, M.D.; George Yancopoulos, M.D.; Eric

J. Rubin, M.D.; Philip Drazen, M.D.; Howard Bauchner, M.D.; Catherine D. DeAngelis, M.D.; Jeffrey P. Henderson, M.D.; Bruce Hall, M.D.; Steven L Liebman, M.D., Richard Stone, M.D. as a legal counsel representative: Jeffrey Rosen, J.D. (former acting Attorney General from December 23, 2020 to January 20, 2021.); representatives from the Association of American Blood Banks (AABB) and the American Red Cross, Dawn O'Connell, J.D., Assistant Secretary for Preparedness and Response, DHHS; etc.

- 4. What could be on the agenda for such a meeting:
 - a. A short course in Clinical Immunology regarding the differences between Active and Passive Immunization presented to the President of the United States and how these agents should be utilized synergistically to end the COVID-19 epidemic in the U.S.A.
 - b. Discussion of how to educate the America public and organize infusion centers around the nation for the EARLY administration of Passive Immunization (Convalescent Plasma, Convalescent Sera, Monoclonal Antibodies, and Monoclonal Antibody Cocktails) and Antiviral agents like Remdesivir. Discussion on how to provide the early administration of Passive Immunization throughout the country. Discuss how to mobilized the nation's blood bank to collect and distribute large quantities of COVID-19 convalescent plasma Fresh Frozen plasma (FFP) as was done during WWII administered initially administrated by Charles Drew, M.D., FACS and the by Eleanor Roosevelt. (Today, in one week, literally with 20 donations daily of COVID-19 Convalescent Plasma (CCP) to the >5000 blood banks throughout the U.S.A., 700,000 units of convalescent FFP can be generated. As there are two doses of 200 ml of "high dose" CCP per FFP unit, 1.4 million units per week are possible. If the FFP is "low dose", doubling the volume to a full unit of FFP (400 ml) will double the polyclonal antibodies administered to an individual (e.g.: 2 or 3 x low dose = one high dose unit of CCP) Most of all, on August 23, 2020 using data from approximately 94,000 units administered late in the disease (the wrong time) by the Mayo Clinic/FDA Expanded Access program (compassionate use of which the data should not have been used) the FDA still concluded that "high dose" was better that "low dose" CCP. Mr. President, would it not seem reasonable that "high dose" is better than NO DOSE!
 - c. Mr. President, with the mortality calculations regarding children under the age of 12 derivable from 1c above, should a school holiday be declared until such time as all the children can be vaccinated? Right now we are essentially putting our unvaccinated children who have not contracted previously COVID-19—thus, being individually immunity naïve to COVID-19--in harms way.

Using the equation: y = 0.0008x - 0.0103 R²=0.8254

One can calculate the estimated mortality by year per 100,000/infected.

(But by the least square fit equation derived from the CDC data of 0-45 years, the predicted age range mortalities really predicts finite mortality from age 13 years and above)

Age	Mortality % Infected	<u>Deaths by Age Group</u> 100,000 in that Age Group
4 yrs	-0.71%	0
5 yrs	-0.63%	0
6 yrs	-0.55%	0
7 yrs	-0.47%	0
8 yrs	-0.39%	0
9 yrs	-0.31%	0
10 yrs	-0.23%	0
11 yrs	-0.15%	0
12 yrs	-0.07%	0
13 yrs	0.01%	10
14 yrs	0.09%	90
15 yrs	0.17%	170
16 yrs	0.25%	250
17 yrs	0.33%	330
18 yrs	0.41%	410
19 yrs	0.49%	490

d. Discussion of the endpoints regarding full approval of all the agents under EUAs that have demonstrated efficacy by appropriate studies (NOT CCP GIVEN LATE IN THE DISEASE AND LACKING AGE STRATIFIED). The FDA can designate as full-fledged drugs and biologics in the treatment of COVID-19 all the present Passive and Active Immunization agents being utilized by shear numbers of administrations of these agents over the last 18 months when they were give early (<72 hours after diagnosis) and when analyzed by age-stratification!

Mr. President, by now you are probably wondering how we got into this mess. Well, frankly, it was a lot of little errors or presentations of selective transparency that cascaded in misleading and misdirecting U.S. Medicine and the US government.

1. The worst error was constructing administration criteria for CCP and Remdesivir at "deaths-door" rather than within 72 hours of diagnosis. On March 24, 2020, the following FDA announcement based on a misinterpretation of a February 2020 Chinese epidemiology paper published in JAMA which never speaks of treatment of COVID-19 was issued that set into motion administration of CCP at the WRONG TIME, initiated a multitude of NIH clinical trials based on the WRONG TIME, and initiate Clinical Practices of administration of CCP at the WRONG TIME that even now have not been rescinded in practice!:

Investigational COVID-19 Convalescent Plasma - Emergency INDs

March 24, 2020

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https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from public health threats including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to doing everything we can to provide timely response efforts to this pandemic and facilitate access to investigational drugs for use in patients with serious or immediately life-threatening COVID-19 infections.

One investigational treatment being explored for COVID-19 involves the use of convalescent plasma collected from recovered COVID-19 patients. It is possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. Although promising, convalescent plasma has not been shown to be effective in every disease studied. It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so. Investigators wishing to study the use of convalescent plasma are encouraged to submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).

Although participation in clinical trials is one way for patients to obtain access to convalescent plasma, these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the expanding COVID-19 outbreak presents, while clinical trials are being conducted, FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency Investigational New Drug Applications (eINDs) for Individual patients under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This does not include the use of COVID-19 convalescent plasma for the prevention of infection.

Healthcare providers interested in the emergency use of investigational COVID-19 convalescent plasma under a single patient emergency IND should consider the following:

COVID 19 Convalescent Plasma

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Additional considerations for donor eligibility should be addressed, as follows:

- · Prior diagnosis of COVID-19 documented by a laboratory test
- . Complete resolution of symptoms at least 14 days prior to donation
- · Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at <a href="https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices/emergency-use-authorizations-
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug-Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

- . Eligible patients for use under expanded access provisions:
 - Must have laboratory confirmed COVID-19
 - Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or
 - · multiple organ dysfunction or failure
 - Must provide informed consent

How to obtain authorization for use of COVID-19 convalescent plasma

- For request that are not highly time sensitive (response from FDA provided within 4 to 8 hours), the requesting
 physician may contact FDA by completing form 3926 (https://www.fda.gov/media/98616/download) and submitting the
 form by email to Covid-19@FDA.HHS.gov.
 - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements of 21 CFR 312.305 and 312.310.
 - The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
 - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.
 - FDA will review the request and, upon approval, FDA will send the requesting physician a confirmatory email that includes the emergency IND number.
- In the event of an emergency that is highly time sensitive (response required in less than 4 hours) or where the
 provider is unable to complete and submit form 3926 due to extenuating circumstances, the provider may contact
 FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
 - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 15 working days of FDA's authorization of the use.

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

⁵ 1Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72†314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Content current as of: 03/24/2020

A British Medical Journal article: https://www.bmj.com/content/bmj/368/bmj.m1256.full.pdf of March 26, 2020 documented for the world this announcement with it attached three references:

- 1 FDA. Investigational covid-19 convalescent plasma—emergency INDs.

 https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber-investigational-covid-19-convalescent-plasma-emergency-inds (When one attempts to use the Wayback machine to find this site, the response is Wayback Machine has not archived that URL.)
- Hixenbaugh M. FDA will allow doctors to treat critically ill coronavirus patients with flood from survivors. NBC News 2020 Mar 24.

 www.nbcnews.com/news/us-news.com/news/us-news/fda-will-allow-doctors-treat-critically-ill-coronavirus-patients-blood-n1167831 which contains the hyperlink: emergency protocols approved by the FDA which directs to: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma (the February 11, 2021 which is the Wayback Machine first "captured". ****Need to research this more as previous with the Wayback Machine pointed to April 8, 2020)
- Palca J. FDA expedites treatment of seriously ill covid-19 patients with experimental plasma. National Public Radio, 24 Mar 2020.

 www.npr.org/sections/coronavirus-live-updates/2020/03/24/820939536/fda-expedite-treatment-of-seriously-ill-covid-19-patients-with-experimental-plasma which contains the hyperlink: emergency protocols approved by the FDA which directs to: www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma (the February 11, 2021 which is the Wayback Machine first "captured". ****Need to research this more as previous with the Wayback Machine pointed to April 8, 2020)

Reference 1 points to a URL that no longer exists and the other two in the body of the article points to the URL: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drugapplications-inds-cber-regulated-products/recommendations-investigational-covid-19convalescent-plasma of February 11, 2021. Previously, if one copied to this URL into the Wayback Machine of the Internet Archive, the initial document in April 2020 which was an expost facto document of April 8, 2020. This represents the now missing "reference" " regarding justification for the criteria incorrectly attributed to the JAMA article of Wu Z, McGoonan JM...(see above)" of the FDA March 24, 2020 announcement. The Incorrect "Eligibility Criteria" criteria was the limiting factor regarding administration of CCP and Remdesivir until September 2, 2020 and August 28, 2020, respectively. The FDA was so "quiet" about these corrections that the VHA issued in November 2020 administration inclusion regarding Remdesivir which was (under the drug name VELKURY) as October 22, 2020 the only FDA fully-approved antiviral (NDA #214787) in the (early) treatment of COVID-19. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf THE WRONG ADMINISTRATION INCLUSION CRITERIA remains the official criteria of the VHA listed on the internet to this day.

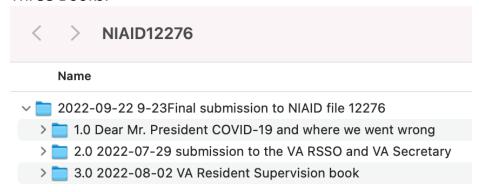
https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf

2. Mr. President, would you consider an Executive Order banning the present practice across the Executive Branch of the U.S. Government of "Overwriting" official documents without official designation of the document(s) rescinded? You could then direct in the Executive Order the reinstatement of the practice that all official documents, policies, directives, and memos of all Departments of the Executive Branch of the U.S. Government document on the face sheet list the previously rescinded document, policy, directive, and/or memo on the present version that it was replacing.—that would be TRUE GOVERNMENTAL TRANSPARENCY. At present, if the replacement document is overwritten electronically and the exact URL is maintained, the replaced/rescinded document can ONLY be located, if the URL has not been changed, by pasting the existing URL into the "Wayback Machine" of the Internet Archive (300 Funston Avenue, San Francisco, CA, 94118, 415-561-6767). This can only occur if the Internet Archive is fortunate to have captured a digital version of the previously overwritten document!

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6.0 1.001 Index of Mr. President COVID-19.pdf Three Books submitted on 9/23/2022

Three Books:



Book 1: Dear Mr. President COVID-19 and where we went wrong



∨ 📄 06 A	Appendices A-H
v 🚞 0	0 Index and 06 final pdf Appendices A-H pdf summary of previous submissions
5	06 final pdf Appendices A-H Index and 291 pages of abridged submission.pdf
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W=	0.1 Index Appendix A
5	202 Time Crucial Independent Variable in COVID-19 Pandemic 06_7-2020 copy.pdf
=	212 Table 1 Demographics (1) copy.pdf
5	213 Table 2 Confirmed COVID-19 Cases copy.pdf
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~ 🚞 A	ppendix Babbr Mayo Clinic Safety Update Should be Completed Phase I Trial TXu2214049
W-	0.1 Index Appendix B
=	321 Classify Mayo Safety Update as Complete1 Trial of COVID-19 Convalescent Plasma.pdf
=	322 Table I - Listing of USA Trials on NIHClinicalTrials 7-6-2020 (1) copy.pdf
-	323 Table II - Mayo Clinic study morbidity mortality and odds of dying copy.pdf
~ 🚞 A	ppendix CCopy of letters sent to 537 Congressional offices August 2020
W -	0.1 Index Appendix C
<u>w</u> -	01 Dear Members of Congress and President Trump 8_23_2020
W -	02 Dear Members of the US House of Representatives 8_28_2020
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=	432 Table I Excerpts from WH briefings etc 11-14-2020 copy.pdf
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∨ 📄 A	ppendix ECorrespondence with VA and NEJM Dec 2020
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=	505.1 Remdesivir VA corr from Nov 2020 to 12_24_2020.pdf
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-	541 Letter to NEJM editor 12_13_2020 (1) copy.pdf
	542 Appendix 1Excerpts regarding Passive Immunization (1) copy.pdf
-	543 Appendix 2ARemdesivir EUAs and NDA no 214787 (1) copy.pdf
=	544 Appendix 2BRE_Remdesivir VA communications 12-15-2020 copy.pdf
=	545 Appendix 2CVACO Remdesivir (VEKLURY) Criteria for Use November 2020 (1) copy.pdf
	546 Appendix 3Ethical Issues (1) copy.pdf
_	ppendix FLetter to Dr. Birx 2-1-2021 et al Appendices A-E as attachments
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_	ppendix GNIH and FDA responses including establish NIAID Case #12276 6-10-2020
	ppolitic 0 1.11.1 and 1.57.1 copolitics including socialists 1.11.15 case in 1.22.7 c o 10 2020
V	Appendix GNIH and FDA responses including establish NIAID Case #12276 6-10-2020
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~	Appendix H Andrus cv and other pertinent info
	01 Andrus SLU cv 8_11_2021
	02 Chapter 3 The Dog Lab copy.pdf
	O3 Chapter 14 Discussions and Reflections copy.pdf
	04 Likert Public opinion polls Sci American 1948 copy
	05 VA November 2020 Remdesivir

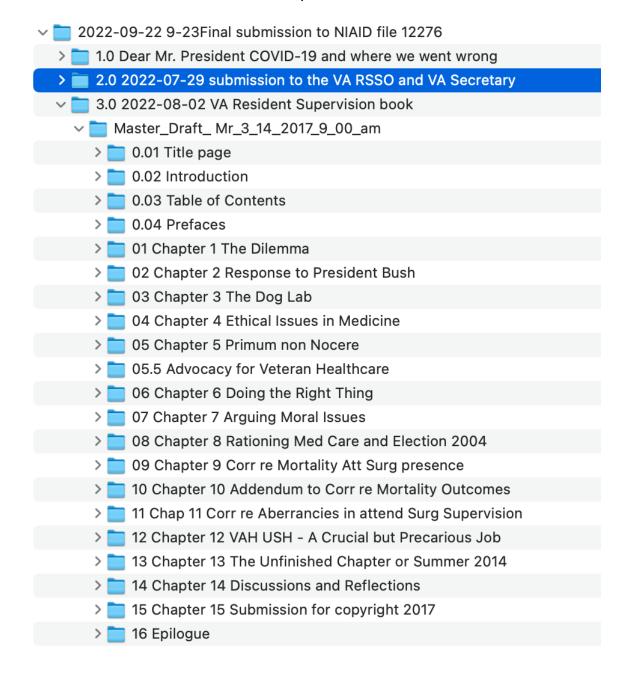
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Book 2: 2.0 2022-07-29 submission to the VA RSSO and VA Secretary



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Book 3: 2022-08-02 VA Resident Supervision book



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Submission 09-12-2023 of BOOK 1 Dear Mr. President TCOVID-19 and Where we went WRONG and treatment of Covid-19 Coronavirus Active Immunization (Prophylaxic production of Endogenous Immunoglobusins (Apr)):266 Pneumonia and Viremia SARS-CoV-2 mRNA vaccines - Production of polyclonal endogenous immunoglobulins against portions of Development of Endogenous Immunoglobulins the spike protein over several weeks prior to infection (e.g. Pfizer, Mederna) COVID-19 after COVID-19 infection: IgM = 5 - 7 days, IgG Passive Immunization (Administration within 72 hours during the viremic phase of = 14 daysExogenous Immunoglobulins (Ab)): COVID-19 Convalescent Plasma: polyclonal Ab (200ml FFP) which can be administered more than once to increase in vivo titers Monoclonal antibodies and antibody cocktails: (Limited by COVID-19 mutational resistant variant to the spike protein Ag) **Antivirals** (Administration within 72 hours during viremic phase): Gilead's Remdesivir: Should administer to anyone turning positive for COVID-19 for 3 days IV; if symptomatic with cough or pneumonia, then treat for 5 days IV Pfizer's pills: Oral treatment twice a day x 3 days to anyone turning positive for COVID-19 Entry through the Nasopharynx nortality per decade age group was horizontal (slope ~ zero) for all groups consist wit

https://ars.els-cdn.com/content/image/1s2.0-S2405650220300691-gr1 lrg.jpg

Nasal Cyto-immunity and Development of IgA: 5 -7 days

Survival vs Death without EARLY treatment: Age Dependent

Cytokine Cascade Treated with Dexamethasone **Bradykinin Storm**

1.002¹²02²02²7¹Pathophysiology and Acute Treatment of COVID-19

8.0 1.003 VA November 2020 Remdesivir (1)

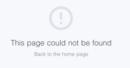
1.003 VA November 2020 Remdesivir (1)

An Example of Electronic Destruction of Documentation

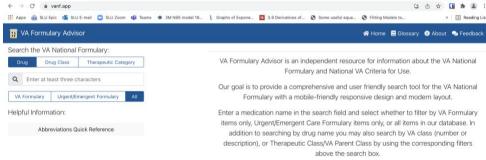
2020-11-01 Echevarria K: Remdesivir (VEKLURY) Criteria for use November 2020. U.S. Department of Veterans Affairs, Veteran Health Administration, VA Pharmacy Benefits Management Services 10P4P.

https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf

In my preparation of my dutiful submission in January 2022, when I attempted to access the URL above on January 5, 2022, the following came up:



When one clicks on: "Back to the home page" https://vanf.app/ one gets:



This is flagrant electronic destruction of official U.S. government documentation by a Service of an Agency of the Executive Branch of the U.S. Federal Government: VA Pharmacy Benefits Management Services 10PAP, Veterans Health Administration, U.S. Department of Veterans Affairs, which is overseen by Carolyn Clancy, M.D., M.A.C.P., VHA Deputy Under Secretary for Health (DUSH) for Discovery, Education & Affiliated Networks (DEAN). Below is the document that has been removed from the Internet that contains erroneous information in the "Inclusion Criteria."

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

Updated version may be found at PBM INTERnet or PBM INTRAnet

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Ex	clusion Criteria
If the	answer to ANY item below is met, then the patient should NOT receive remdesivir Treated for COVID-19 as an outpatient AST or ALT > 5 times the upper limit of normal Hospitalized patients but NOT requiring supplemental oxygen* Concomitant use of hydroxychloroquine or chloroquine Current eGFR < 30 mL/min**
Inc	lusion Criteria
The f	following must be fulfilled in order to meet criteria for remdesivir Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
Su	pplemental Information
or wh	mmended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving no remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration erapy has not been given
adjud **Patik recon espe loca ***Ri	In hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be disated on a case by case basis ents with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not numerated by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, ecially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on all guidance. I guidance. I guidance is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with a patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19
	ared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program ager, VA Pharmacy Benefits Management Services 10P4P

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9.0 1.004 2022-03-09 Once viewed as a promising COVID-19 treatment copy.pdf 1.004 2022-03-09 Once viewed as a promising COVID-19 treatment copy

2022-03-09 Rubi R: Once viewed as a promising COVID-19 treatment, convalescent plasma falls out of favor. JAMA network, **JAMA** Published online March 9, 2022. https://jamanetwork.com/journals/jama/fullarticle/2790074?guestAccess

In the pandemic's initial dark days, physicians and patients and their families were desperate for effective COVID-19 treatments. (1.) They didn't yet have monoclonal antibodies or antiviral pills to lessen the ravages of the disease, so many turned to a therapy more than a century old.

At the very least, they figured, convalescent plasma², donated by people who'd recovered from COVID-19, couldn't hurt, and the SARS-CoV-2 antibodies it was presumed to contain could enhance patients' defenses against COVID-19.

- (2.) "There was a preconceived notion of efficacy," H. Clifford Lane, MD, deputy director for clinical research and special projects at the National Institute of Allergy and Infectious Diseases, said in a recent interview. https://www.niaid.nih.gov/about/h-clifford-lane-md-bio 3
- (3.) Three reports from Wuhan, China, published in 2020 in *JAMA* (https://jamanetwork.com/journals/jama/fullarticle/2763983)^{4,5}, the *Proceedings of the National Academy of Sciences* (https://www.pnas.org/doi/10.1073/pnas.2004168117) ⁶, and the *Journal of Medical Virology* (https://onlinelibrary.wiley.com/doi/10.1002/jmv.25882)⁷, showed that patients' viral load decreased and their symptoms improved following infusions of convalescent plasma. But the studies involved only a total of 21 patients; the authors of all 3 articles noted that clinical trials were needed to confirm the findings.
- (4.) Nevertheless, while trials were being planned, US hospitals began infusing patients with COVID-19 with convalescent plasma through the US Food and Drug Administration's (FDA's) Expanded Access Program (EAP). Approximately 94 000 (https://www.uscovidplasma.org/)8 people hospitalized with COVID-19 in the US had received convalescent plasma infusions by August 2020, when the FDA ended https://newsnetwork.mayoclinic.org/discussion/expanded-access-program-for-convalescent-plasma-discontinues-enrollment-as-fda-authorizes-its-emergency-use/) the EAP and authorized the golden liquid for emergency use.
- (5.) A December 2021 analysis of EAP data (https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003872)¹⁰ in *PLOS Medicine* demonstrated convalescent plasma's safety in patients hospitalized with COVID-19—the incidence of serious adverse events was less than 1%. But because the study didn't include a control or comparator group, "the data should not be used to infer definitive treatment effects," the authors noted.

(6.) As other COVID-19 treatments became available, convalescent plasma's early promise didn't pan out in randomized clinical trials. "I don't think convalescent plasma is a first-line therapy at this point," Kevin Schulman, MD, a professor of medicine at the Stanford University School of Medicine who has studied the treatment, said in an interview.

Panic Instead of Science?

(7.) Convalescent plasma wasn't associated with clinical benefit in a recent *JAMA*Network Open meta-analysis

(https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2788377)¹¹ that pooled findings from 8 randomized clinical trials involving 2341 hospitalized patients breathing without the aid of mechanical ventilation, 1231 of whom received the treatment.

- (8.) A UK trial (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00897-7/fulltext) published too recently to be considered for inclusion in the meta-analysis reached a similar conclusion. It randomized 11 558 hospitalized patients—5% of whom were receiving invasive mechanical ventilation upon randomization—to receive usual care plus convalescent plasma or only usual care. Researchers found that convalescent plasma did not improve survival or progression to ventilation.
- (9.) In addition, a recently published (https://www.nejm.org/doi/10.1056/NEJMoa2103784) 13 multicenter placebo-controlled trial randomized 511 high-risk outpatients with COVID-19 who came to emergency departments within 7 days of symptom onset. The study found that convalescent plasma didn't prevent disease progression.

"We've moved on," said Schulman, a coauthor of the emergency department trial. "Convalescent plasma is a great thing to think about very early in a pandemic."

(10.) Instead of providing an untested treatment to tens of thousands of patients in the EAP, multiple, large clinical trials could have been conducted, Schulman said. But, he added, a "huge amount of desperation" early in the pandemic "turned into panic, not into science."

Large clinical trials, with 2500 patients apiece, could have answered questions that still remain, such as identifying the optimal dose and timing of convalescent plasma treatment and which patients are likely to benefit, Schulman said.

(11.) "You could easily argue we underdosed patients" in his trial, Schulman acknowledged. "Our trial was the best we could do at the time."

All in the Timing?

(12.) Arturo Casadevall, MD, PhD, a leader of the National COVID-19 Convalescent Plasma Project (https://ccpp19.org/about/index.html)14, isn't ready to abandon a

treatment he's championed since penning a *Wall Street Journal* op-ed (https://www.wsj.com/articles/how-a-boys-blood-stopped-an-outbreak-11582847330) about it in February 2020.

"In the spring of 2020, I really thought that convalescent plasma was a safety raft to new therapies that would be available in the fall," Casadevall, chair of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health, said in a recent interview.

(13.) Casadevall said he would have liked to conduct clinical trials with some of the patients enrolled in the EAP, but funding wasn't available. Instead, he took a different approach to try to assess convalescent plasma's efficacy: He tracked the number of convalescent plasma units that blood banking organizations dispensed to hospitals per admission and COVID-19 deaths in the fall of 2020. (14.) Casadevall and his collaborators found (https://elifesciences.org/articles/69866)¹⁶ a strong inverse correlation between convalescent plasma use per COVID-19 hospital admission and deaths from the disease occurring 2 weeks after admission.

The problem with the randomized trials is that they didn't treat patients soon enough to make a difference, Casadevall said.

- (15.) Only trials in which patients receive convalescent plasma early in their infection could be expected to show a treatment benefit, he explained. By the time patients require hospitalization for COVID-19, the horse is already out of the barn. At that point, Casadevall said, inflammation is the problem, so anti–SARS-CoV-2 antibodies wouldn't help slow disease progression.
- (16.) (Similarly, no anti–SARS-CoV-2 monoclonal antibody product has been authorized (https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/)¹⁷ for patients with severe COVID-19.) The National COVID-19 Convalescent Plasma Project has posted critiques of Schulman's study, the UK trial, and other research on its website (https://ccpp19.org/news/index.html)¹⁸.

(17.) Casadevall coauthored a recent

multicenter trial (https://www.medrxiv.org/content/10.1101/2021.12.10.21267485v1.fu ll.pdf)¹⁹ that randomized 1225 outpatients whose COVID-19 symptoms had begun within 8 days before enrollment. The study, which hasn't been peer-reviewed, found that early administration of high-titer SARS-CoV-2 convalescent plasma reduced hospitalizations over the next 28 days by 54% compared with control plasma from donors who had not had COVID-19.

(18.) "High titer convalescent plasma is an effective early outpatient COVID-19 treatment with advantages of low cost, wide availability, and rapid resilience to variant emergence from viral genetic drift in the face of a changing pandemic," Casadevall and his coauthors concluded.

Limiting Its Use

Despite Casadevall's favorable finding, recently updated guidelines from the World Health Organization (WHO), the FDA, and the Infectious Diseases Society of America (IDSA) recommend only limited use of convalescent plasma, if that.

(19.) On February 8, 2022, IDSA strongly recommended against (https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt---convalescent-plasma-2022-02-03.pdf) ²⁰ using convalescent plasma in patients hospitalized with COVID-19. Among ambulatory patients with mild to moderate disease who are at high risk of progression to more serious symptoms and have no other treatment options, infusing high-titer COVID-19 convalescent plasma within 8 days of symptom onset is better than not infusing it, according to the guideline, which described this as a conditional recommendation with low certainty of evidence.

- (20.) The FDA's most recent revision (https://www.fda.gov/media/141477/download)²¹ of the Emergency Use Authorization (EUA) for COVID-19 convalescent plasma, published December 28, 2021, limits treatment with high-titer COVID-19 convalescent plasma to patients who have immunosuppressive disease or are receiving immunosuppressive treatment.
- (21.) Randomized clinical trials and observational studies show that convalescent plasma is unlikely to be associated with clinical benefit in immunocompetent individuals with COVID-19, according to the FDA.
- (22.) Interestingly, the WHO recommends against its use (https://www.who.int/news/item/07-12-2021-who-recommends-against-the-use-of-convalescent-plasma-to-treat-covid19#:~:text=Convalescent%20plasma%20is%20a%20transfusion,while%20it%20ha s%20significant%20costs.)²² for patients who *aren't* severely ill, calling the evidence for that position "certain." Convalescent plasma should be used only within clinical trials for severe and critical patients with COVID-19, the WHO said in December 2021.
- (23.) In a letter to the *BMJ*, Casadevall and coauthors urged the WHO to reconsider, saying that the organization "avoided digging below the surface to ask critical questions about treatment timing, study populations, and antibody titre" of the convalescent plasma in the trials it considered.

For now, demand for convalescent plasma is low because the clinical trial findings in hospitalized patients have persuaded many physicians that it won't benefit any patients, Casadevall said. On top of that, he said, "Medicine has gotten used to working with therapies that are very well-defined. Plasma is a therapy where physicians are uncomfortable because every unit is different. To many people, that just doesn't feel right."

(24.) Lane is among those people. "It's not a uniform product," he noted. Assays suggested by the FDA measure only antibodies to the spike protein of 1 variant, so it's difficult to know the true level and nature of antibodies in a unit of convalescent plasma, Lane said.

And it's virtually impossible to judge a unit of plasma by its donor, Lane said. "Typically, the sicker you are, the better your antibodies." Younger people also tend to generate more antibodies than older people, he added. However, "the immune response to SARS-CoV-2 is highly variable."

(25.) Other COVID-19 treatments are standardized, so physicians can know exactly what they're giving patients, Lane said. "If you have an at-risk ambulatory patient with symptoms, you can give them Paxlovid [nirmatrelvir and ritonavir, Pfizer's antiviral pill], you can give them remdesivir. You can reduce their risk of being hospitalized 80% to 85%, and you know what you've given."

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Article Information

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Conflict of Interest Disclosures: Dr Schulman reports receiving personal fees from Novartis and from Frazier Healthcare Partners. Dr Casadevall reports that he is involved in convalescent plasma clinical trials at Johns Hopkins and serves on the scientific board of SAB Biotherapeutics, an antibody company.

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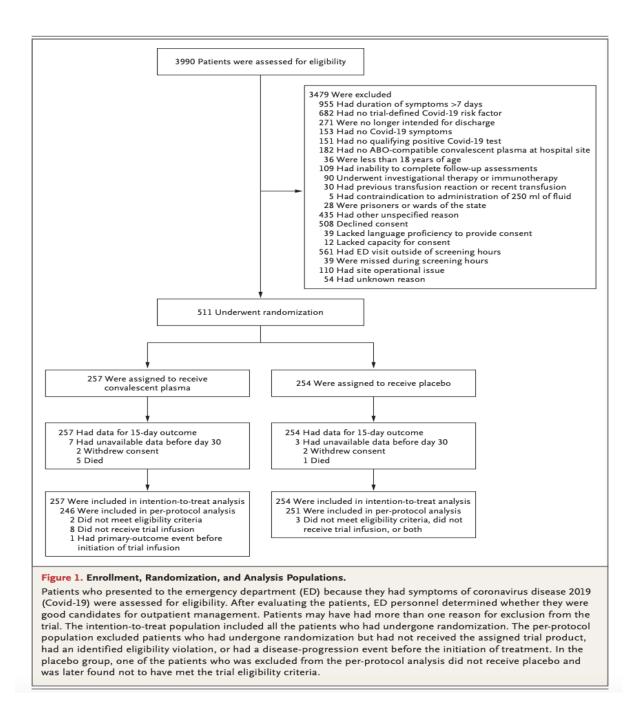
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 (https://clinicaltrials.gov/ct2/show/NCT04381936
) had as its Inclusion Criteria: (i) Hospitalised, (ii) SARS-CoV-2 infection (clinically suspected or laboratory confirmed), and iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial.
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Figure 1 from the article is the following:



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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total_U.S. Cases since 1/22/2020	Total_U.SD eaths since 1/22/2020	
2020-02-24	Wu Z, McGoogan JM: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) Outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. Doi:10:1001/jama.2020.2648. https://jamanetwork.com/journals/jama/fullarticle/2762130 (THIS IS THE ARTICLE IN WHICH OFFICIALLY THE U.S. FDA INCORRECTLY BASED THE ELIGIBILITY CRITERIA FOR THE ADMINISTRATION OF COVID-19 CONVALESCENT PLASMA that remained official from March 24, 2020 to September 2, 2020.	16		
2020-03-01	Retroactive EMTALA waivers (Ref 344, 347)	32	1	
2020-03-02	WH meeting which did not include the AMERICAN RED CROSS. Dr. Schleifer confuses "passive vaccination" with "passive immunity" failing to mention Convalescent Plasma as an EARLY TREATMENT (<72 hours) (Ref: 332, 333, 334, 335, 336 two minutes of WH meeting (https://www.youtube.com/watch?v=31i6p stzW8), (Ref337)	55	6	
2020-03-13	President Trump declares Public Health Emergency (PHE). (Ref 347, 350)	2219	51	
2020-03-14	China sends experts to Italy (Ref 345)	2978	58	
2020-03-19	Surgeon General Adams Public Service Announcement (PSA). (Ref 352) & Johns Hopkins documents China sends 90 tons CCP to Italy (Ref 353)	13663	266	
2020-03-24	FDA (WRONG) Inclusion Criteria based on wrong interpretation and thus wrong application (Ref 362, 373)	56714	1033	
2020-03-25		68841	1366	
2020-03-26		86662	1783	
2020-03-27		105253	2305	
2020-04-01	Norah O'Donnell of CBS News states to Dr Fauci: With all due respect it does seem like so much of this we're making it up as we go along. (Ref 385, 413)	227898	6996	
2020-04-04	FDA/Mayo Clinic Expanded Access Protocol for COVID-19 (Ref 393)	324341	11593	
2020-04-08	FDA announces FDA/Mayo Clinic Expanded Access with Inclusion criteria based on WRONG TIME of administration. (Ref 403, 404)	446505	19737	
2020-04-16	Wired, News Archives UK: The blood of coronavirus survivors could help cope with the pandemic. https://www.wired.co.uk/article/coronavirus-blood-plasmatrials (Ref 413)	683357	37487	
2020-04-24	President Trump overshadows CCP talking about possible IV disinfectants (Ref: 425)	918954	55195	
2020-05-01	President Trump announces Remdesivir. (Ref 431-434, 437, 441, 445,448)	1115889	68513	
2020-05-14	Joyner et al safety report of the first 5000 patients in FDA/ Mayo Clinic Expanded Access (compassionate use) protocol (Ref 464)	1424855	89558	
2020-06-02	European Blood Alliance: COVID-19 Convalescent Plasma (Ref 480, 481)	1828871	109582	
2020-06-08	Dr. Fauci speaks with JAMA (Ref 486) and Dr. Andrus submits: Time: The Crucial Independent Variable of the COCVID-19 Pandemic, US Copyright Office Txu002199029. (Ref 487)	1956980	114050	
2020-06-09	Kara Harris responding for Dr. Fauci establishes NIH NIAID Case #12276. (Ref 490)	1977325	114959	
6/19/20	K. McEnany in WH press conference reiterating that "Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promisingthis has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages" (Ref 495)	2222188	121748	
2020-06-28	DHHS Secretary Azar pleads on CNN for COVID-19 Convalescent Plasma and then pushes to dismantling of the ACA. (Ref 503)	2557309	126496	

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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers 20-07-07 Casadevall, Joyner, Pirofski: SARS-CoV-2 viral load and antibody responses: the case for convalescent plasma therapy. (Ref 508). And Regeneron receives an additional \$450 million to produce monoclonal antibody cocktail (Regeneron had received at least \$400 million for R&D earlier in 2020) Ref 316, 317, 336 348, 351, 374, 478, 491, 509, 510, 511, 549			
2020-07-07				
2020-07-19	Joyner et al safety report of the first 20,000 patients in FDA/ Mayo Clinic Expanded Access (compassionate use) protocol (Ref 521)	3768319	141176	
2020-07-22	Dr. Andrus submits: The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma US Copyright Office Txu002214049. (Ref 522)	3965007	144026	
2020-07-30	President Trump visits the American Red Cross to highlight need for convalescent plasma during COVID-19. (Ref 527, 528, 529, 530), 531, 532, 534, 535, 536, 538, 539, 541, 542)	4485123	152751	
2020-08-12	Two Washington U. doctors lead national effort to study new COVID-19 treatment, in which Highly Unethical statement made regards to research coercion: "If you have a 50% chance of getting either the stuff or nothing, which would you choose?" (Ref 543) and Joyner et al 3-month update on Mayo Clinic / FDA Expanded Access (compassionate use) Protocol (Ref 544)	5213811	165984	
2020-08-23	Presiden Trump News Conference day before RNC to promote COVID-19 Convalescent Plasma (CCP) essentially <u>PUTS AN END TO</u> THE FDA / MAYO CLINIC EXPANDED ACCESS PROTOCOL. (Ref 551) Research and Academic Medicine disapproves and Trump team does damage control [and FDA proceeds] (Ref 552, 553, 554, 555, 556, 557, 558, 560, 561, 562, 563)	5721417	176027	
2020-08-24	Dr Andrus on 8-23-2020 submits letter to U.S. Senate: Thousands of Americans are needless dying because the FDA is illegally ignoring PL 115-176 – The Right to Try Law1,2 and COVID-19 Convalescent Plasma has NOT been given as Prophylaxis and Early after COVID-19 positivity conversion. Letter mailed to President Trump and the offices of the U.S. Senate. [In the attached CD: 06 Appendices A-H copy/01 Dear Members of Congress and President Trump 8 23 2020]	5755517	176460	
2020-08-28	etter to the Offices of the U.S. House of Representatives. [In the attached CD: 06 Appendices A-H copy/02 Dear Members of the US louse of Representatives 8_28_2020] Ref 568. and FDA Chief Scientist Hinton removes WRONG time administration for lemdesivir. (Ref 567). MOST AMERICANS DON'T EVEN KNOW OF THIS!		180874	
2020-09-02	FDA removes WRONG time administration for COVID-19 Convalescent Plasma (CCP). (Ref 570). MOST AMERICANS DON'T EVEN KNOW OF THIS!	6129854	184879	
2020-09-16	European Blood Alliance: Support-E European project on COVID-19 convalescent plasma. EU Commission allocates 4M grant for SUPPORT-E. (Ref 581)	6660686	195708	
2020-09-25	Pau et al, Ann of Internal Med: [This is the NIH's justification of merging Phase I (safety) trials with Phase II (efficacy) trials so as to circumvent completely ever applying PL-115-176: The Right to Try Law with regards to COVID-19 Convalescent Plasma but also any future investigational drug or biologic ad infinatum. This obfuscation by the NIH is tantamount to justifying repeated violations of PL-115-176 and is ethically shameful!]. (Ref 592)	7051336	202732	
2020-10-02	President Trump, Rudy Guiliani, Chris Christy, and Ben Carson, M.D. positive for COVID-19 and are treated with monoclonal Ab or Abcocktail and Remdesivir (Ref 602, 603, 604, 605, 606, 615, 617, 618, 620, 621, 622, 626, 629, 636, 640, 680, 688, 689, 690, 694, 705)	7347629	207669	
2020-10-07	Eli Lilly asks FDA for authorization of monoclonal Ab and Regeneron follows with request for monoclonal Ab cocktail. (Ref 611, 624, 625, 630, 638, 639, 641, 642, 643, 644, 649, 651, 653, 654, 655, 656, 657, 658, 659, 661, 664, 665, 668, 671, 675, 676, 677, 686, 687, 696, 701)	7562786	210779	
2020-10-08	Beigel, et al: Remdesivir for the treatment of Covid-19 – Final Report. NEJM.org, October 8, 2020. (Ref 613, 650)	7620994	211752	

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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total_U.S. Cases since 1/22/2020	Total_U.SD eaths since 1/22/2020		
2020-10-16	0-10-16 Hinton update of Remdesivir EUA. (Ref 627) and again update on 10/22/2020 (Ref 631) the same day the Infectious Diseases division of the FDA gives OK to VEKLURY with a New Drug Authorization (NDA #214787). (Ref 632)		217721		
2020-10-22	Hinton update of Remdesivir EUA. (Ref 627) and again update on 10/22/2020 (Ref 631) the same day, Dr JJ Farley , M.D. the Infectious Diseases division of the FDA gives OK to VEKLURY with a New Drug Authorization (NDA #214787). (Ref 632, 633, 634)	8444916	222482		
2020-10-31	Liu, et: Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. Nature Medicine 2020 November. (Ref 646)	9177121	230489		
2020-11-01	VACO publishes WRONG ILLNESS guidelines for Remdesivir 3 MONTHS after withdrawn by FDA and two weeks after Remdesivir is a prescription drug NDA #214787. (Ref 647) which is later removed from the Internet tantamount to destruction of Federal Documentation	9255213	230997		
2020-11-09	Pfizer announces vaccine. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against	10193449	239251		
2020-11-18	Andrus CH: 1 Dear Mr President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. U.S. Copyright Office, 2020-11-18, TXu002232947. (Ref 669)		251335		
2020-11-24	Simonovich, et al: A randomized trial of convalescent plasma in Covid-19 Severe Pneumonia, PlasmAR ClinicalTrials.gov number, NCT04383535. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2031304, November 24, 2020, 1-11. (Ref: 679 THIS STUDY WAS RCT GIVEN IN SEVERE COVID-19 WHICH WAS THE WRONG TIME.	12694436	261351		
2020-12-13	Andrus CH: Letter to the Editor of the New England Journal of Medicine regarding treatment with and synergy of Passive Immunization regarding the SARS-CoV-2 virus infection. ***The editors of NEJM ignored the letter but on January 6, 2021 published the landmark article (appropriately age stratified and COVID-19 Convalescent Plasma given within 72 hours of diagnosis): Libster, et. al.: Early high-titer plasma therapy to prevent severe Covid-19 in older adults, ClinicalTrials.gov, NCT04479163. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2033700, January 6, 2021, 1-9. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true (Ref: 691)	16443123	302726		
2020-12-20	Andrus: E-mail submitted to Dr. Richard Stone, M.D., Chief Medical Executive (acting Under Secretary of the Veterans Health Administration), regarding the WRONG INCLUSION CRITERIA which contradicted the FDA directive of early administration in the course of COVID-19 disease (<72 hours from diagnosis) going forward from August 28, 2020 to the present, regarding Remdesivir (an FDA -approved licensed drug: NDA# 214787). This ERRONEOUS DIRECTIVE was still published on the Internet as of October 3, 2021—not having been retracted by the Veterans Health Administration (VHA)—SHAME ON THE VHA! The URL is no longer available. https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf What use to be at this U.S. Department of Veterans Affairs website is the following page that directed the administration of Remdesivir at the wrong time. (Ref 697,		321791		
2020-12-24	Andrus CH: E-mail directed to the NEJM the VHA, etc. was ignored. (Ref 700)	18827673	333123		
2021-01-06	Libster, et al: Early high-titer plasma therapy to prevent severe Covid-19 in older adults, ClinicalTrials.gov, NCT04479163. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2033700, January 6, 2021, 1-9. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true (Ref 706). <i>LANDMARK ARTICLE</i>	21553506			
2021-01-12					

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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total_U.S. Cases since 1/22/2020	Total_U.SD eaths since 1/22/2020	
2021-01-13	Joyner et al: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med, January 13, 2021, at NEJM.org; then republished N Engl J Med 2021; 384:1015-1027. https://www.nejm.org/doi/full/10.1056/NEJMoa2031893 (Ref 713)	23270675	389809	
2021-01-21	Eli Lilly announcement to stockholders: Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. https://natap.org/2021/COVID/020321_02.htm (Ref 726)	24821319	415411	
2021-01-24	Face the Nation: Margaret Brennan interviews Deborah Birx, M.D. Face the Nation, CBSNews. The abridged version that aired on Face the Nation on Sunday morning, January 24, 2021: https://www.youtube.com/watch?v=odklJGnhvhU (Ref 730)	25329732	424538	
2021-02-01	Andrus: Dear Dr. Birx:	26485208	448299	
	On March 24, 2020, while there was much discussion and debate about COVID-19 convalescent plasma and the possible development of monoclonal antibodies against COVID-19, U.S. Medicine and the Government failed to explain to the American public the differences and individual utilities of Active Immunization (vaccines to stimulate patient antibody production) and Passive Immunization (provision of convalescent plasmas, convalescence sera, and immunoglobins from other species providing already formed antibodies (IgM, IgG, and IgA) against the virus in COVID-19 immunologically naïve patients immediately within 72 hours of diagnosis (testing positive). (Ref 738)			
2021-02-04	Hinton: EUA-update regarding COVID-19 Convalescent plasma. February 4, 2021 (Ref 740)	26851874	459586	
2021-02-13	Trump acquitted of inciting insurrection Ref 761, 762)	27758422	483536	
	Promising monoclonal antibodies (Ref 763, 764)	27942629	487277	
2/18/21	Katz LM: (A Little) Clarity on convalescent plasma for Covid-19. Initially published on January 13, 2021) This editorial was republished in the N Engl J Med, 2021 Feb 18; 384 (7): 666 – 668. https://www.nejm.org/doi/full/10.1056/NEJMe2035678 (Ref 770). and FDA revises EUA for COVID-19 Convalescent Plasma. WebMD. John Whyte, M.D., Chief Medical Officer at WebMD interviews Peter Marks, M.D., PhD, Director for the Center for Biologics Evaluation and Research at the U.S. FDA: FDA revises EUA for COVID-19 convalescent plasma. https://www.webmd.com/coronavirus-in-context/video/peter-marks-plasma. (Ref 771)	28083898	492242	
2021-02-24	Biden JR: Notice on the Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic. February 24, 2021 – Presidential Actions https://www.whitehouse.gov/briefing-room/presidential-actions/2021/02/24/notice-on-the-continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic/ (Ref 775)		504565	
2021-02-26	The Biden administration buys 100,000 doses of a combination antibody treatment for high-risk Covid-19 patients. The New York Times, Feb 26, 2021. https://www.nytimes.com/2021/02/26/world/bamlanivimab-etesevimab-eli-lilly-monoclonal-antibodies.html (Ref 780)	28644508	509110	
2021-02-27	NIH halts halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms – Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health announcement is: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms (Ref 785). Results upon which discission is based are not released until Nov 18, 2021)	28715319	510623	
2021-03-08	Blood center to phase out CCP donations—Due to strong inventory, decline in COVID-19 hospitalization rate, Blood Center will phase out COVID-19 Convalescent Plasma donations March 26, 2021. (Ref 792)	29225673	524042	

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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total_U.S. Cases since 1/22/2020	Total_U.SD eaths since 1/22/2020	
2021-03-18	Joyner et al: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021 Mar 18; 384 (11): https://www.nejm.org/doi/full/10.1056/nejmoa2031893 and https://www.nejm.org/doi/pdf/10.1056/NEJMoa2031893?articleTools=true (Ref 797)	29786820	536571	
2021-03-29	CNN: America's pandemic dead deserve accountability after Birx disclosure. CNN politics. https://www.cnn.com/2021/03/29/politics/coronavirus-deborah-birx-donald-trump-joe-biden/index.html (Ref 803)	30450787	546417	
2021-04-12	Regeneron: Phase 3 Prevention Trial Showed 81% Reduced Risk of Symptomatic SARS-CoV-2 Infections with Subcutaneous Administration of REGEN-COV TM (casirivimab with imdevimab). https://investor.regeneron.com/node/25016/pdf (Ref 811, 812, 813, 814, 815, 838, 858)	31388097	558760	
2021-06-04	Casadevall, et al: Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality. eLife 2021; 10e69866. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205484/pdf/elife-69866.pdf (Ref 861)	33462671	592705	
2021-08-23	FDA approves first COVID-19 Vaccine (Ref 922)	38101123	626720	
2021-09-20	CDC, COVID-19: Pfizer-BioNTech COVID-19 vaccine overview and safety (also known as COMIRNATY). https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Pfizer-BioNTech.html (Ref 961, 962, 963)	42370019	674301	
2021-10-04	NIH: Francis Collins to step down as NIH director by year's end. POLITICO. https://www.politico.com/news/2021/10/04/francis-collins-nih-step-down-515114 (Ref 981, 1064)	43935571	702382	
2021-10-08	Verify977): Claim that the federal government is rationing monoclonal antibodies. KHOU 11 https://www.khou.com/article/news/verify/verify-federal-government-is-rationing-monoclonal-antibodies/285-aae3608f-c439-4d4f-83de-4e6c76365081 (Ref 988)		711213	
2021-11-05	5 Pfizer: Pfizer's novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in Interim Analysis of Phase 2/3 EPIC-HR study. https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate (Ref 1008)		752815	
2021-11-18	Korley FK, et al: Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO Clinical Trials.gov number, NCT04355767.] https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true (Ref 1022). RESULTS OF SIREN-C3PO Publishes results 11 months after FDA stops CCP collection throughout the nation. Recruitment for study and poor unpowered statistics!	47583696	767709	
2021-11-19	2021-11-18 Kimball S: Biden administration buys \$10 million courses of Pfizer Covid treatment pill in \$5 billion deal. https://www.cnbc.com/2021/11/18/biden-administration-buys-10-million-courses-of-pfizer-covid-treatment-pill.html (Ref 1025)	47709964	769479	
2021-11-21	Face the Nation: response, CBS News. Fauci says Fauci says he'd be "astounded" if there wasn't an autopsy on what went wrong in COVID response, CBS News. (Attempt of accessing this website on Google: Fauci Brennan Face the Nation on November 22, 2021 was unsuccessful but "autopsy" provided by yahoo): https://www.yahoo.com/now/fauci-says-hed-astounded-wasnt-150638991.html (Ref 1031, 1035, 1036, 1037)		770202	
2021-11-29	Pfizer CEO confident Covid treatment pill will be effective against omicron variant. https://www.cnbc.com/2021/11/29/pfizer-ceo-confident-covid-treatment-pill-effective-against-omicron-variant.html (Ref 1038)		777915	
2021-12-03		49043954	787061	

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Date	Treatment Milestones after the 3/1/2020 EMTALA waivers	Total_U.S. Cases since 1/22/2020	Total_U.SD eaths since 1/22/2020	
2021-12-07	WHO: WHO recommends against the use of convalescent plasma to treat COVID-19. December 7, 2021.	49455723	791118	
	https://www.who.int/news/item/07-12-2021-who-recommends-against-the-use-of-convalescent-plasma-to-treat-covid-			
	19#:~:text=Convalescent%20plasma%20is%20a%20transfusion,while%20it%20has%20significant%20costs. (Ref 10-51)			
2021-12-16	NIH: Anti-SARS-CoV-2 Monoclonal Antibodies, Table A. (Last updated 16, 2021)	50581783	803656	
	https://www.covid19treatmentguidelines.nih.gov/tables/table-a/ According to the Wayback Machine there are digital copies of			
	updates going back to August 6, 2021 with the NIH "last update" is August 4, 2021.			
	https://web.archive.org/web/20210806205833/https://www.covid19treatmentguidelines.nih.gov/tables/table-a/ (Ref 1060, 1069)			
2021-12-19	Fauci: Pfizer's possibly game-changing Covid-19 pill won't be widely available for 'months."	50946835	806519	
	https://www.forbes.com/sites/marisadellatto/2021/12/19/fauci-pfizers-possibly-game-changing-covid-19-pill-wont-be-widely-			
	available-for-months/?sh=1bc7e423cc30 (Ref 1066)			
2021-12-20	Senefeld JWf, et al: Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national	51188108	808071	
	registry study. PLOS Medicine 2021 December 20; 1-28.			
	https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003872 (Ref 1067)			
2021-12-22	FDA authorizes first oral antiviral for treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-	51618251	814170	
	covid-19-u pdate-fda-authorizes-first-oral-antiviral-treatment-covid-19 (Ref 1071, 1072, 1076, 1095, 1099)			
2022-01-07	K Kavanaugh: Miscellaneous Order (12/22/2021) for oral arguments before the U.S. Supreme Court on Friday, January 7, 2022 in	59672311	837409	
	application 21 A244: NAT. FED'N OF INDEP. BUS., ET AL. V. DEPT. OF LABOR, OSHA, ET AL. and application 21 A247: OHIO, ET AL. V.			
	DEPT. OF LABOR, ET AL. https://www.supremecourt.gov/orders/courtorders/122221zr2_f20h.pdf (Ref 1073, 1084, 1087, 1088,			
	1104			
2022-02-16	Andrus CH: Thank you letter to Gilead Sciences for providing the reference regarding the date of completion of Phase 1 remdesivir trial.	78350913	929485	
	(Ref 1131)			
2022-02-22	Trump praises Putin's 'genius" incursion into Ukraine (Ref 1132, 1134, 1135, 1136, 1137)	78820149	939160	
2022-02-28	Pfizer CANNOT EVEN MENTION Paxlovid's name in advertisement as drug is under an EUA: iSpot.tv: Pfizer, Inc. TV Spot, 'Move	79207551	950422	
	Fast: Oral Treatment. https://www.ispot.tv/ad/bAea/pfizer-inc-move-fast-oral-treatment (Ref 1138, 1146, 1151, 1160, 1179)			
2022-03-09	Rubin R: Once viewed as a promising COVID-19 treatment, convalescent plasma falls out of favor. JAMA network	79561996	963397	
	https://jamanetwork.com/journals/jama/fullarticle/2790074?guestAccess (Ref 1144)		, , , ,	
2022-05-12	Tin A: 1 million COVID deaths: Pandemic's tragic toll in U.S. extends far beyond the numbers. CBS News	82479277	1001596	
_0 00 12	https://www.cbsnews.com/news/covid-deaths-1-million-us-pandemic-toll/ (Ref 1184)	02.7,277	1001000	

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11 4.01 Significant Dear Mr. President draft letters.pdf

The following draft letters are part of this section:

12.0 0.1 2022-01-25 Hogan re National Blood Shortage

13.01.0 2021-11-02 Dear President Biden and ACS 2021 President Freischlag

14.0 2.0 2021-10-18 Dear Mr. President -- Did USA Medicine abandon the People 15.0 Numbering error – no chapter

16.0 3.0 2021-10-16 Patient states Government Lied

17.0 4.0 2021-10-02 What Would C. Everett Koop M.D. FACS say?

18.0 5.0 1.0 2022-8-24 Dear Mr President submission coverletter

19.0 6.0 2021-09-25 How Did We Get Into This Mess?

20.0 7.0 2021-09-19 Timeline of U.S. Government Regarding Passive Immunization 21.0 8.0

2021-09-12 NIAID 12276 confirmed and Fauci 4-2018 and 8-24-2021

22.0 9.0 2021-08-22 One year after EUA COVID-19 Convalescent Plasma

23.0 10.0 2021-08-12 Triage

24.0 11.0 2021-07-25 Please stop the NIH and the FDA from ignoring Public Laws 25.0 12.0

2021-07-22 Early Timeline to 8/12/2020--Missing the ETHICS boat

26.0 13.0 2021-06-27 Passive Immunization has been around for 135 years!

27.0 14.0 2021-06-18 EARLY administration of POLYCLONAL CCP OR pooled CCS

28.0 15.0 2021-02-27 EARLY<72 hrs Passive Immunity + Antiviral for ALL COVID-19 infected

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12.0 0.1 2022-01-25 Hogan re National Blood Shortage.pdf



0.1 2022-01-25 Hogan re National Blood Shortage.pdf

DEPARTMENT OF VETERANS AFFAIRS
Medical Center
John Cochran Division
915 N. Grand Boulevard
St. Louis, MO 63106

January 25, 2022

Michael R. Hogan
Deputy General Counsel, General Law
Designated Agency Ethics Official
Office of General Counsel
Department of Veterans Affairs
810 Vermont Ave, NW
Washington, DC 20420
202.461.7713 (Direct)
michael.hogan@va.gov

Re: Blood Shortage and EMTALA NIAID Case# 12276

Dear Mr. Hogan:

On Sunday, January 23, 2022, I was informed by the Chief of Surgery, St. Louis VAMC, that the St. Louis VAMC had been notified by the St. Louis Blood Bank (a member of ImpactLife – formally Mississippi River Valley Regional Blood Center)¹ that it cannot supply any blood to the St. Louis VAMC during this National Blood-shortage Crisis.² The Chief of Surgery emphasized in his phone call that all scheduled OR cases for Monday (except those where no incision was being made, e.g.: exams under anesthesia, EUAs, etc.) would be cancelled. At the time, he stated that I and every physician who gets a call from an outside hospital to transfer a Veteran patient would have to consider whether or not to accept the Veteran patient in transfer. On the following day, the Chief of Surgery emphasized that before we accepted any patient in transfer, we should get him involved--which we have done and have accepted at least one Veteran patient when contacted by a referring institution since.

Under EMTALA: Emergency Medical Treatment and Labor Act of COBRA, Consolidated Omnibus Budget Act of 1986, PL-99-272^{3,4}, any patient presenting to any hospital ER is guaranteed the right of the following:

- 1. Stabilization / Resuscitation
- 2. Diagnosis
- 3. Appropriate disposition

On March 13, 2020, President Trump declared a National State of Emergency regarding COVID-19, Proclamation 9994.^{5,6} The President directed then DHHS Secretary Azar to put in place that which would be consistent in directing this National State of Emergency. On March 13, 2020, DHHS Secretary Azar suspended some of the guarantees of EMTALA retroactive to March 1, 2020.⁷ Over the last 23 months, I personally know of instances where patients have been denied their rights guaranteed under EMTALA in the denial of transfer, rationing of immunologics or antivirals, or withholding of appropriate medical care in the non-treatment of COVID-19. (As an aside: This is the reason why the NIH has not "completed" any Phase I study (Safety Clinical Trials)—so the Right to Try Act, PL115-176, cannot not be implemented⁸; and

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all drugs and biologics, except for Remdesivir (VEKLURY, NDA 214787)⁹ and Pfizer-BIONTech COVID-19 mRNA Vaccine, (COMIRNATY, BLA 125742/0)¹⁰, are still under EUAs (Emergency Use Authorizations¹¹ for <u>Unapproved Drugs</u> or Biologics by the FDA).

The St. Louis VAMC is a Tertiary VA Medical Center. As with all VAMCs, the VHA physicians and surgeons are mandated to address any Veteran patient in referral from any hospital. In short, what is now playing out may be in contradiction to the VA's mandate from President Lincoln: ...to care for him who shall have borne the battle and his widow and his orphan...¹². Several months ago at a previous COVID-19 spike, I was notified by the St. Louis VAMC Chief of Surgery that the St. Louis VAMC had been activated by FEMA¹³ to accept in transfer patients--veterans and civilians--which was a directive that expanded the patient care mandate of the VA.

Mr. Hogan, this National Blood-shortage Crisis² has magnified the medical/legal ethical dilemmas during COVID-19 posed to VHA physicians and surgeons and all physicians in the U.S.A condoning medical nihilism of *de facto* rationing and withholding of treatment. The rights of Americans (both Veterans and Civilians) are potentially being infringed upon and/or violated as guaranteed under PL-99-272, EMTALA^{3,4} (which may still be suspended as I am not sure DHHS Secretary Azar's directive has yet to be rescinded⁷); PL-115-176, The Right to Try Act⁸; and the Preamble to the Constitution of the United States of America¹⁴:

We the People, in Order to form a more perfect Union, establish Justice, insure domestic Tranquility, provide for the common defense, **promote the general Welfare**, and secure the Blessings of Liberty to ourselves and our Posterity, do ordain and establish this Constitution for the United States of America.

As you are the VA Designated Agency Ethics Official¹⁵, I am providing my concerns to you so that you might share these concerns with VA General Counsel Richard A. Sauber, JD; VHA Acting Under Secretary for Health Steven Lieberman, M.D.; VA Secretary Denis McDonough; DHHS Secretary Xavier Becerra; Attorney General Merrick Garland, JD; NIAID Director Anthony Fauci, M.D. PhD; former NIH Director Francis Collins, M.D., PhD; and President Biden. Thank you so much for your consideration of this submission.

Respectfully,



Charles Andrus, MD, FACS

Chief, Unit II (SLU) Gen Surg, Surg Svc, St. Lo...

Charles Andrus, M.D., F.A.C.S.

Chief, Unit II (SLU section) General Surgery, Surgical Service, St. Louis VAMC Professor, Department of Surgery, Saint Louis University School of Medicine JCVAMC office phone 314-652-4100 ext: 54463

Beeper 314-491-2417 Home: 314-455-9482

Pam, my wife's cell: 314-809-9634

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- 6. Biden JR: Notice on the Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic. February 24, 2021 Presidential Actions <a href="https://www.whitehouse.gov/briefing-room/presidential-actions/2021/02/24/notice-on-the-continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic/#:~:text=On%20March%2013%2C%202020%2C%20by,and%20safety%20of%20the%20Nation.
- 7. Azar AM: Waiver or modification of requirements under section 1135 of the Social Security Act. Public Health Emergency.

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- 11. U.S. Food and Drug Administration: Emergency Use Authorization.

 https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
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With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan—to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

- 13. FEMA (Federal Emergency Management Agency) of the Department of Homeland Security. https://www.fema.gov/
- 14. Madison J: The Constitution of the United States of America. https://www.archives.gov/founding-docs/constitution
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 https://extanps2.org/201/Presiden.nsf/PAS+Index/240REDEAC38845E48525868D

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13.0 1.0 2021-11-02 Dear President Biden and ACS 2021 President Freischlag

150 Emerald Green Court St. Louis, MO. 63141 314-455-9482

November 24, 2021

Joseph Biden
President, United States of America
The White House
1600 Pennsylvania Ave
Washington, D.C. 20500
(202) 456-1414

Julie A. Freischlag, M.D., F.A.C.S.
President, American College of Surgeons
Dean, Wake Forest School of Medicine
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RE: NIAID Case #12276: Advocacy for Balanced/Synergistic Active and Passive Immunization in the Treatment of Coronavirus SARS-CoV-2 (COVID-19)

Dear U.S. President Biden and ACS President Freischlag:

Please excuse my forwardness of this submission; but, to put it bluntly, we of the United States of America need figuratively to send every physician, nurse, medical technologist, pharmacist, and scientist of the FDA, the NIH, the CDC, the PHS, Academic Medicine, all Universities, and the Editors of every Medical Publication in the World back to high school chemistry or college Chem 101.

I. The equation below is a simple titration:

$$C_1 \times V_1 = C_2 \times V_2$$

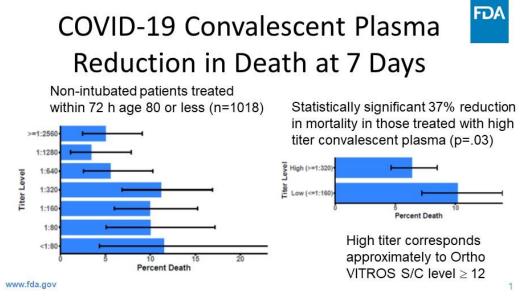
where C is the concentration of a solution (e.g.: moles of substance, titers of antibodies, etc.) and V is volume of the solution (e.g.: ml, L, oz, etc). The equation above is the mathematical construct for the basis of all titrations--including Clinical Immunology:

Antibody titer₁ x Volume₁ =Antibody titer₂ x Volume₂

Since August 2020, the FDA's EUAs regarding CO\VID-19 Convalescent Plasma and all reports from the NIH, CDC, PHS, and the Press have proclaimed to the United States that:

High Dose COVID-19 Convalescent Plasma is better than Low Dose COVID-19 Convalescent Plasma —and was graphed by individuals of the FDA (Graph 1) on August 23, 2020:

Graph 1: FDA documentation justifying the first EUA for <u>EARLY</u> ["Non-intubated patients treated within 72 h age 80 or less (n=1018)] COVID-19 Convalescent Plasma of August 23, 2020:



A dose of COVID-19 Convalescent Plasma is 200 ml (~7 fluid ounces, ½ of a unit) of COVID-19 Convalescent Fresh Frozen Plasma (CC-FFP). Thus, from Graph 1, Table 1 is constructed:

Table 1: Conversion Low Dose COVID-19 Convalescent Plasma to High Dose COVID-19 Convalescent Plasma (CC-FFP) by increasing administration volume:

Titer of a Dose (200 ml) of CC-FFP	C1: Relative Polyclonal Antibody Units (RPAU)	V1: Std Volume of CC-FFP (200 ml = 1/2 unit of CC-FFP) std dose vol	RPAU x 200 ml	C1 x V2= RPAU x 400 ml RPAU x 400 ml = 1 unit of CC-FFP	C1 x V2= RPAU x 800 ml RPAU x 800 ml = 2 units of CC-FFP	C1 x V2= RPAU x 1600 ml RPAU x 1600 ml = 4 units of CC-FFP
Very low titer <1:80 dilution	<80					
Low titer 1:80 dilution	80	200	16,000	32,000	64,000	128,000
Low titer 1:160 dilution	160	200	32,000	64,000	128,000	256,000
Low titer - 1:320 dilution	320	200	64,000	128,000	256,000	512,000
High titer 1:640 dilution	640	200	128,000	256,000	512,000	1,024,000
High titer 1:1280 dilution	1280	200	256,000	512,000	1,024,000	2,048,000
High titer ≥ 1:2560 dilution	2560	200	512,000	1,024,000	2,048,000	4,096,000

The shaded areas represent "High Dose administrations" or conversions to "High Dose administrations" of COVID-19 Convalescent Plasma by infusing a full unit of CC-FFP, doubling the units administered or quadrupling the units administered (e.g.: 1 unit, 2 units, 4 units) so as to exceed threshold of survivability at a range of 3%-5% when the Relative Polyclonal Antibody Units x volume equals or exceeds 128,000. Since August 23, 2020, the FDA, the NIH, etc. have touted to the American people that: By the **EARLY** (<72 Hours from diagnosis) **TREATMENT** of a newly acquired infection of coronavirus SARS-CoV-2 (COVID-19) with High Dose COVID-19 Convalescent Plasma (CCP) **ONLY**: "HIGH DOSE COVID-19 Convalescent Plasma is BETTER than LOW DOSE COVID-19 Convalescent Plasma" with **better survival**. Thus, from the FDA's graph above:

- (1) for (high dose) titers of 1:640 dilution to > 1:2560 dilution, **200 ml** (1/2 CC-FFP unit) IS MOST protective (more efficacious) titers (~3-5% death rate)
- (2) for an (intermediate dose) 1:320 dilution (~12% death rate), **400 ml** (1 CC-FFP unit) would be equivalent to the absolute neutralizing antibodies in 200 ml of a 1:640 dilution
- (3) for (low dose) titers of 1:160 and 1:80 dilutions (~10% death rate), **800 ml and 1600 ml, respectively** (2 CC-FFP units and 4 CC-FFP units, respectively) are adequate.

By increasing the administration volumes of Low Dose COVID-19 Convalescent Plasma or by concentrating (pooling multiple units) Low Dose COVID-19 Convalescent Plasma into COVID-19 Convalescent Serum, effective Passive Immunization with mortality rates of 4%-5% averaged across all age groups should have been accomplishable. Unfortunately, the FDA officially permitted administration of CC-FFP only in hospitalized patients; and the majority of the >772,000 CC-FFP doses all going to hospitalized patients were at the WRONG TIME--late in the disease--during the cytokine cascade and the bradykinin phases from at least April 2020 to the present. Can you imagine the decrease in mortality if the CC-FFP had been given HD AS AN IMMEDIATE, EARLY TREATMENT FOR NEWLY DIAGNOSED COVID-19 in all patients with COVID-19 as is implied by the FDA in the graph above (Graph 1)!?!?! A ½ unit of (Fresh Frozen Plasma) FFP (1 "dose") is ~200 ml; one unit of FFP is ~400 ml; and two units of FFP are ~800 ml. As a Vascular Surgeon, Dr. Freischlag Julie, have you ever observed the unlikely fluid-overload of an adult patient strictly due to the tremendous volume of only 1 or 2 units (400 ml or 800 ml) of Fresh Frozen Plasma (FFP) administration? – I doubt it (Julie, please excuse my sarcasm as we have used as surgeons FFP in blood component volume expansion when required throughout our professional lives with minimal complications.)!

II. ANOTHER CONCEPT IN RESEARCH THAT THE FDA, THE NIH, ETC. FAILED TO

ADDRESS: Controlling a crucial Independent Variable in their statistical calculations
THAT HAS A TREMEDOUSLY WIDE RANGE OF RESULTANT OUTCOME:

AGE

Throughout the last 18 months, Passive Immunization has not been presented to the general public as a synergistic equal partner in the fight of COVID-19 with Active Immunization. Thus, when COIVD-19 Convalescent Plasma was declared *Investigational* on March 24, 2020, no prospective, organized plan of **EARLY** immunotherapy treatment for all who contracted COVID-19 was established. From past epidemics over the last 120 years, the U.S. Government knew that **EARLY** doses of **exogenous neutralizing antibodies** (Passive Immunization/Convalescent Plasma/Convalescent Serum) would increase survival <u>better than NO DOSE</u>. In March 2020, the people of the U.S.A. were essentially abandoned by the Medical/Industrial/Governmental Complex by withholding **EARLY** treatment with COVID-19 Convalescent Plasma essentially being non-existant.

When most Medical Research Trials are initiated, a well-defined experimental group is chosen in which to study an independent variable with multiple dependent variables (resultant variables). In COVID-19, the Experimental "Treatment" Group by default *de facto* became the population of the United States who became infected with COVID-19 BUT THE U.S. GOVERNMENT FAILED TO RECOGNIZE THIS. With U.S. Clinical Trials being initiated regarding immunologic treatments, the FDA, the NIH, other branches of the U.S. Department of Health and Human Services, Medical Academia, and Pharmaceutical Research in March 2020, WRONGLY attempted to treat only those with the risk factors for poor outcomes in COVID-19: ≥ 65 years of age, obesity, hypertension, and diabetes and based Inclusion Criteria on at death's door disease in the individual.

· Eligible patients for use under expanded access provisions:

- o Must have laboratory confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale... 2/3

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

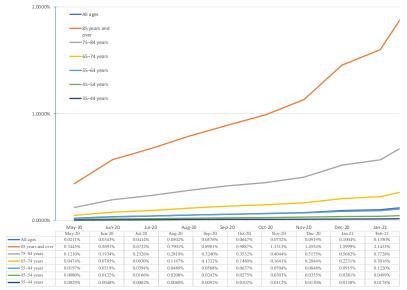
- multiple organ dysfunction or failure
- Must provide informed consent

¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

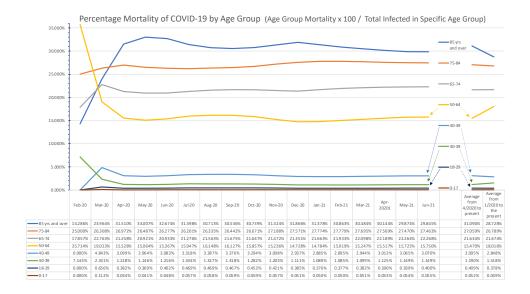
What was not realized was that by AGE Decade Groups in adults (e.g.= 45-64, 65-74, 75-84, 85 and above) the plotting of Death with AGE Decade Groups is an independent, steeply-increasing, linear variables (Graph 3) that would obscure and skew outcome results in relatively small prospective studies when age was not stratified.

Inadvertently, over most of the U.S. COVID-19 epidemic, infected COVID-19 were prohibited from being treated **EARLY during the viremic phase of COVID** by FDA EUA's that relegated CC-FFP to ONLY HOSPITALIZED patients. The natural mortality outcomes by age groups biweekly were documented by the CDC but never analyzed regarding longitudinal trends:

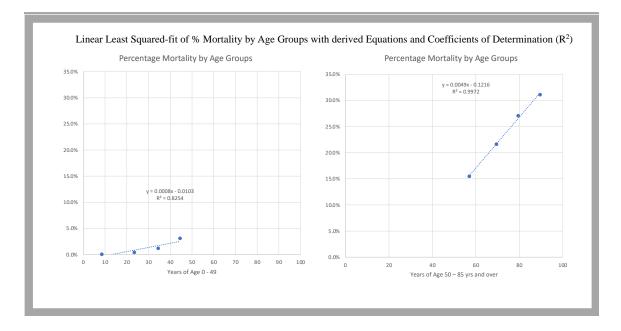
Graph 2: Percentage of the Population of Each Age Group vs Total Deaths involving COVID-19 (U07.1) reported by the CDC



Graph 3: Percentage of the Population of Each Age Group vs Deaths of Each Age Groups involving COVID-19 (U07.1) calculated from the CDC reports:



Over a 14-month reporting period, mortality within age groups over those infected in those age groups demonstrated longitudinal, near-linear-stable relationships with increasing percentage mortality by age. Performing a least-squares fit of Decade Age Group percentage mortality (y-axis) versus Age Groups (x- axis) yields to distinct linear relationships for the 0 year to 44 year group and 45 year to >85 year group. (Graph 4)



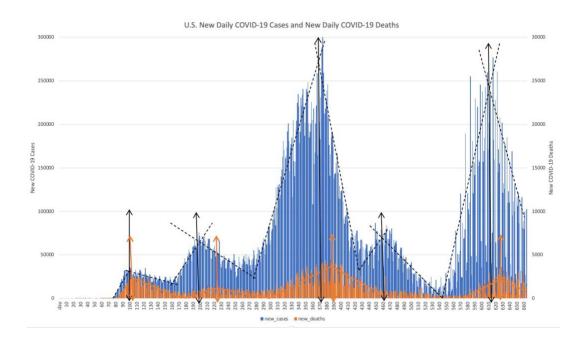
Graph 4: Linear Least squares-fit of % Mortality by Age Groups:

Thus, mortality within age group is defined by two equations with the adult group increasing in percentage mortality 1% every two years:

$$0-45$$
 years: $y=0.0008x-0.0103$ $R^2=0.825$ 46 years -- >85 years: $y=0.0049x-0.1216$ $R^2=0.997$

Thus, in the Fall of 2020, when each of the following individuals were treated **EARLY** with monoclonal antibodies (Passive Immunization) the mortality risk was: former President Trump, 74 yrs: 24.1%; former Governor Christie, 58 yrs: 16.3%; former NY Mayor Giuliani, 76 yrs: 25.1%; and former HUD Secretary Dr. Carson, 69: 22.1%. Why was not the rest of the American population who upon confirmed diagnosis of COVID-19 offered some form of **EARLY Passive Immunization (COVID-19 Convalescent Plasma or Serum or Monoclonal Antibodies or Antibody Cocktails)?** Did you know that Regeneron's Monoclonal Antibody Cocktail is being sold and administered in India to those who can pay (50,000 Rupees which is ~\$800)? While the U.S. Government funded the R&D for the development of the Regeneron Monoclonal Antibody Cocktail in early 2020, did you know that it is being marketed in India by Roche International? Is this to circumvent the promise Regeneron made to the U.S. Government to market in America first and foremost?

III. The Pathophysiology has not been well defined and Long-term predicted population outcomes minimized:



*****Need to discuss logarithmic decline approaching zero cases asymptoticly***

Throughout the last 18 months, the United States people as individuals have--to varying degrees and at irregular times—experienced and/or expressed the five Stages of Elisabeth Kübler-Ross's *On Death and Dying*. Chapter VIII which immediately follows the chapters on the five Stages: Chapter III: Denial and Isolation; Chapter IV: Anger; Chapter V: Bargaining; Chapter VI: Depression; and Chapter VII: Acceptance, IS ENTITLED: *HOPE*.

Over the last 18 months, ALL AMERICANS to some extend have been discouraged, denied, or stripped of <u>HOPE</u> with the *de facto* WITHHOLDING of the early treatment of COVID-19 (within 72 hours of diagnosis) with Passive Immunization! Mr. President, while it may not be my place to direct you:

Why not call Drs. Fauci and Collins into the Oval Office and have them explain the basics of Clinical Immunology—not the high-tech Molecular Biology and rigorous demands of "Evidence-based Medicine" that the people of the U.S.A. have been subjected to for 18 months; but rather, how in daily Clinical Medical Practice, the physician, confronted with an infection of a novel virus in the individual before him/her, should **ALWAYS** TREAT—when available--**EARLY** (within ~72 hours) with Passive Immunization and Antivirals during the <u>viremic phase</u> of an infection like coronavirus SARS-CoV-2 (COVID-19). Drs. Fauci and Collins will probably question 10% of what I have stated above; BUT, in the other 90%, they will concede that this is appropriate Medical Reasoning and Recommended Care.

One of my Veteran patients stated to me over the phone: I will not get vaccinated! When I asked why? With regards to COVID-19, he simply stated that our government had lied to us. What could I say?—his statement was and is true. We, in the Federal Government, since March 2, 2020 have been parties to shading-the-truth, distraction and flim-flam, cheating, and outright lying to the American people. Elisabeth Kübler-Ross's stage of **Anger** has been borne out in the last 18 months in various ways privately and publicly. Unfortunately, it is a natural human response when people are scared and have been misled. Mr. President give the American people **HOPE**. As Dr. Fauci stated in his *White House* slide show of August 24, 2021, monoclonal antibodies (e.g., agents of Passive Immunization) **have been underutilized**.

Mr. President: Every man, woman, and child who contracts coronavirus SARS-CoV-2, should receive treatment as soon as they are diagnosed with COVID-19 with some form of **PASSIVE IMMUNIZATION** and an **ANTIVIRAL**.

Dr. Freischlag Julie, you and I had the privilege to have as our mentors: Robert Condon, M.D., F.A.C.S., Vallee Willman, M.D., F.A.C.S., and C. Rollins Hanlon, M.D., F.A.C.S. All were Surgeons of Integrity and Honesty—both in their patient Advocacy in general and specifically in their focused, appropriate, indicated provision of clinical care in the treatment of each and every patient who presented before them. They epitomized the highest aspirations and stated goals of the American College of Surgeons throughout their lives that you, I, and every Fellow of the American College of Surgeons of our generation pledged:

...I pledge myself to pursue the practice of surgery with scientific honesty and to place the welfare of my patients above all else; to advance constantly in knowledge; and to render willing help to my colleagues, regard their professional interest, and seek their counsel when in doubt as to my own judgement. ...Moreover, I promise to deal with each patient as I would wish to be dealt with were I in his position. ...

The American College of Surgeons once again needs to reaffirm its promise to the American people in their fight with COVID-19. Julie, please express to President Biden, your personal knowledge of me as we were former VA Chiefs of Surgery of the Clement J. Zablocki VAMC and Edward Hines, Jr. VAH, respectively. While we were not always in the good graces of the VISN 12 Director during our tenures, we always strove to do what was right for each and every Veteran patient. Julie, tell President Biden of my sense of duty, my tenacity, and, frankly, that I'm not going away--for it is our duty as Surgeons to strive for what is right for all patients and to advocate for each and every patient appropriate medical TREATMENT. As Francis W. Peabody mentioned a century ago:

...for the secret of the care of the patient is in caring for the patient.

Two decades ago, my proudest and most humbling moment in my fight to prevent unsupervised resident-performed surgery inadvertently tolerated by VHA Handbook 1400.1: "Level 3: Attending surgeon is immediately available" in Andrus v VA, Case #03-3162, U.S. Court of Appeals for the Federal Circuit, was when VA Regional Counsel in an interrogatory stated: The problem with Dr. Andrus is that he thinks President Lincoln is personally speaking to him. As you can probably guess, I immediately responded with something like the following – President Lincoln speaks to all of us in his Second Inaugural Address.

In this present time where the American people are uncertain of their Government's intentions and response to COVID-19:

- 1) COVID-19 infected individuals are fighting a virus when--if unvaccinated, non-responding to the vaccines, or immunosuppressed--are <u>immunologically naïve</u> to the virus
- 2) and political-partisan fingers and opportunistic, conflicted-in-interest businesspersons; are all-too-quick to point blame:
- 3) we need to take to heart that which President admonished all Americans for all times to do for their fellow Americas on March 4, 1865:

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for this widow, and his orphan—to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

WHAT FOLLOWS IS A MORE-INDEPTH ANALYSIS AND RECOMMENDATIONS DERIVED FROM THESE ANALYSES:

As last month was that of the Annual American College of Surgeons Clinical Congress, I am submitting this letter to both of you in an attempt to draw from the past: The American College

of Surgeons (ACS) ever-available assistance for the United States Government in addressing pressing and critical medical problems of the day. Over the last 18 months, while the USA and the world have addressed many facets of COVID-19, US Medicine and the US Government have obfuscated without clear definition, specific application, and appropriate synergism in the Treatment of COVID-19 (Passive Immunization and antivirals) rather than the eggs-in-onebasket approach by seemingly-solely promoting Prevention (Active immunization--Vaccines) to the American public. Goal-modeling of continued excellence in education as professed by the American College of Surgeons (ACS) over the last century resulted in the ACS exclusively providing organized accreditation, standardization, and credentialing of Surgeons and Hospitals throughout the first half of the 20th Century for the United States and Canada. In an organized, deliberate fashion, the transitioning of those responsibilities were accomplished in 1938 with the transferring of surgeon credentialling to the American Board of Surgery; and the changeover of hospital accreditation to the Joint Commission on Hospital Accreditation in 1951. Today, I plead that the ACS should again offer to the U.S. Government and U.S. Medicine recommendations regarding the Medical-Industrial complex's legal and ethical adherence to policies, oversight, and laws regarding:

- (1) experimental/investigational drugs and biologics,
- (2) proscription of coercion in clinical trials, and
- (3) denunciation of overriding ever-present conflict-of-interests in medical research.

Over the last 18 months, U.S. Medicine's struggle with COVID-19 has been a piecemeal, disorganized addressing of the pathophysiology of coronavirus SARS-CoV-2--often with conflicting Research Medicine and Governmental policies and processes that have not promoted expedient resolution of the U.S. epidemic. The national focus was and has been directed to in-the-future Vaccines (promoting endogenous immunoglobulins generated in vaccinated individuals—Active Immunization) in deference to the immediately-available (atthe-time of contraction of the disease) of exogenous immunoglobulins administration in treatment with COVID-19 Convalescent Plasma (Passive Immunization). Although both monoclonal antibodies and polyclonal antibodies are Passive Immunization agents and thus equivalent in mode of action, over the last 18 months COVID-19 Convalescent Plasma has been relegated to the scrapheap with the promise of monoclonal antibodies to being available. In March 2020, United States Medicine went down a path where EARLY exogenous antibody treatment with COVID-19 Convalescent Plasma would be de facto withheld from anyone contracting COVID-19, designating it as an Investigational Biologic (instead of a biosimilar biologic) on March 24, 2020, and then mandating that it be administered LATE in the disease the WRONG Time--based on a misinterpretation and misapplication of a Chinese epidemiology paper. Instead of EARLY appropriate administration during the initial viremic stage of COVID-19 with Passive Immunization (COVID-19 Convalescent Plasma), the misinterpretation of the Chinese epidemiology paper resulted in the administration of Passive Immunization during the later cytokine cascade and bradykinin storm phases at the far-end (deaths-door) of the individual's COVID-19 disease process which was the WRONG ADMINISTRATION TIME when CCP and monoclonal antibodies are much less effective:

· Eligible patients for use under expanded access provisions:

- o Must have laboratory confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale... 2/3

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

- multiple organ dysfunction or failure
- Must provide informed consent

¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

(During his ACS Franklin Martin Memorial Lecture of October 25, 2021, Dr. Fauci quoted these authors appropriately regarding distribution of patient severity-of-illness in Slide 17: "Spectrum of Disease Among 44,672 Individuals with Confirmed COVID-19, China." Unfortunately, Dr. Fauci failed to mention the erroneous FDA Eligibility Criteria for COVID-19 Convalescent Plasma (CCP) developed from this misapplication that persisted in all FDA documentation until September 2, 2020, when it was quietly removed from all FDA documents and publications.). This misapplication continues to be de facto applied to this day in last week's reporting of the SIREN-C3PO Clinical Trial.

Prior to the first EUA regarding COVID-19 Convalescent Plasma announced by President Trump at The White House press conference on August 23, 2020 (the day before the Republican National Convention), there were five Expanded Access programs registered with the NIH Clinical Trials https://clinicaltrials.gov administering CCP under "Compassionate Use" status at the WRONG time during the individual's LATE phases of the disease: (1) cytokine cascade and (2) bradykinin storm which are at the far-end of the individual's struggle in this COVID-19 disease continuum: NCT04358211, Tulane Medical Center; NCT04420988, Rutgers New Jersey Medical School; NCT04445207, Univ. Massachusetts Medical School; NCT04374370, AdventHealth, Orland NCT04372368, the State of Colorado; and the Mayo Clinic/FDA Expanded Access program recruiting over 2,700 hospitals, NCT04338360.

The days after I mailed 637 letters to the Offices of the Senators and Congresspersons of the U.S. Congress, the FDA withdrew quietly the INCORRECT Eligibility Criteria listed above both for the antiviral Remdesivir on August 28, 2020, and for CCP on September 2, 2020. The FDA Chief Scientist, RADM Denise Hinton, R.N., M.S., included the evolutionary history regarding Remdesivir emphasizing the requirement for EARLY administration in all subsequent EUAs regarding Remdesivir until October 22, 2021, when another section of the FDA (Office of Infectious Diseases) declared Remdesivir (VELKURY) a prescription drug, NDA 214787. Unfortunately, the WRONG assumption of the LATE administration of Remdesivir is still pervasive today. The Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs codified the WRONG eligibility criteria and posted it on the Internet in November 2020, after it was no longer INVESTIGATIONAL! Several weeks later employing this post facto INCORRECT LATE administration protocol, the St. Louis VAMC Infectious Diseases division denied RemdesIvir to one of my newly diagnosed surgical patients with COVID-19 citing the November 2020 VHA Internet posting. Even though I notified collectively Richard Stone, M.D., VHA Chief Medical Executive, the FDA, the NIH, the editors of *The New England Journal of* Medicine and a host of others, the VHA has continued the posting of this INCORRECT administration time to this day and VHA HSR&D has published at least three monographs employing data when Remdesivir is administered at the wrong time! This posting is absolutely contradictory to that which Dr. Fauci asserted about Remdesivir during the Franklin Martin Memorial Lecture on October 25, 2021.

Even though its origins date back to Louis Pasteur (rabies vaccine) and von Behring who was awarded the first Noble Prize regarding plasma therapy in Physiology or Medicine a century ago, the importance and possible advantage of EARLY administration of Passive Immunization in the TREATMENT of COVID-19 Convalescent Plasma (CCP) has been minimized with the administration at the LATE WRONG time to greater than 720,000 people. The NIH in March 2021, advised discontinuation of the collection and administration of CCP in an underpowered, skewed outpatient trial clinical (SIREN-C3PO) [NCT0435767] and denounced CCP in application of this underpowered, prospective clinical trial that did not age-stratify the statistical analyses when those that contracted COVID-19 have an \sim 0.5% linear annual increase in mortality from age 50 onward demonstrated in a least-squares fit of CDC data over the last year (R² = 0.997) leading to the following derived equation:

$$y = 0.0049 \text{ x} - 0.1216$$
 $x = age of patient in years, $y = \%$ mortality by age$

Although Dr. Fauci's interview in 2018, his slide show virtually from *The White House* of August 24, 2021, and his virtual presentation before the October 25, 2021, mentioned polyclonal and monoclonal antibodies, the fact that they are all agents of exogenous antibodies with diminishing usefulness when administered <u>LATE</u> in the disease process (during the cytokine and bradykinin storms). **EARLY Administration is most effective** upon contraction of the virus (< 72 hours) in which immunologically the individual is naïve to COVID-19 or overall immunocompromised (immunosuppressed as in transplantation patients or non-responsive to

vaccination in such groups as cancer patients—especially the monoclonal gammopathy of Multiple Myeloma).

On October 14, 2020, the NIAID curtailed the Eli Lilly research of its monoclonal antibody on hospitalized patients because it was not age-stratified and the monoclonal antibody had been given at the WRONG LATE time in hospitalized patients. All resultant published research and EUAs for monoclonal antibodies have been restricted to non-hospitalized patients that have not demonstrated the parameters of the WRONG eligibility criteria that existed for CCP from March 24, 2020, to September 2, 2020. While the EUAs issued by RADM Hinton regarding CCP encouraged EARLY administration, the same EUAs restricted CCP administration ONLY to hospitalized patients. While monoclonal and polyclonal antibodies are all Passive Immunologic agents, the inadvertent distinctions/restrictions in TIMING administration have unfavorably promoted monoclonal antibodies and denigrated convalescent plasma. In the aggregate, these administrative maneuvers have limited availability, capacity, and effectiveness of Passive Immunization by CCP administration EARLY to ALL who contract coronavirus SARS-CoV-2.

Rather than focusing on treatment with Passive Immunization, Research Medicine and the agencies of the U.S. Department of Health and Human Services (DHHS) focused on <u>prevention</u> only (vaccines) to reach a baseline state of the disease (Herd Immunity).

This confused, convoluted application of Clinical Immunology has been contributory to the resultant loss of over 700,000 American lives. From March 2, 2020, to the present, the U.S. has gone down as series of proverbial "rabbit holes" driven by failure of Research Medicine to adhere to time-established previous standard treatments regarding the addressing of new emerging viruses within an immunologically naïve populous with Passive Immunization that has its foundational origins with Pasteur and von Behring over a century ago. The FDA lacked appropriate adherence to their own posted definitions and policies regarding (1) expanded access (compassionate use—which is prohibited by standard research protocols to be used to generate research data and draw research conclusions); (2) phases of clinical trials; and (3) appropriate transitioning from designated investigational drugs/biologics to "new" official prescription drugs/biologics even after the safe administration of hundreds of thousands of doses of these drugs/biologics. The NIH (with FDA acquiescence) merged the concept of Phase I (safety) and Phase II (efficacy) Clinical Trials into a continuum thus avoiding designating the official "Completion" of Phase I Clinical Trials which perpetuated the abuse of the "Emergency Use Authorizations (EUA)" of the drugs/biologics as investigational only and thus violating American patient rights under the Right to Try Act (PL-115-176). Such methodologies resulted in the de facto nullification of the rights of all Americans to be able to request EARLY (within 72 hours) treatment after the confirmed diagnosis of COVID-19 infection in each individual. These processes were orchestrated by multiple agencies of the U.S. Department Health and Human Services at the direction of the Trump administration in "Operation Warp Speed" through B.A.R.D.A. permitting to prevail throughout the governmental agencies: ignorance, arrogance, and research conflict-of-interests and promoting corporate and personal greed to prevail at the expense of millions of Americans. In short, the FDA, the NIH, the CDC, and the PHS failed to promote an organized EARLY therapeutic immunotherapy plan (Passive Immunization) since

March 2, 2020, that should have been available to all people of the U.S.A. immediately at the contraction of the disease as it was available one year ago to former President Trump, former Governor Christie, former HUD Secretary Dr. Carson, and former N.Y. Mayor Giuliani. The non-uniform, organized availability of EARLY treatment with Passive Immunization of individuals infected with coronavirus SARS-CoV-2 has resulted in a multitude of tragic/horrific individual outcomes that have been detrimental to our entire U.S. society.

Mr. President the following are my recommendations to you from me, a Federal Physician and Surgeon, that should be considered for implementation to address and rectify that which I have stated above:

- 1. By Presidential Executive Order, electronic overwriting and changing URLs of all policies, documents, and directives (PDD) which is a form of OBSTRUCTION OF JUSTICE by all Agencies and Departments of the Executive Branch of the Federal Government should be PROHIBITED. Any subsequent PDD that rescinds and thus replaces a previous PDD should document the previous PDD on the face sheet of the new PDD documenting the prior URL and any change in the URL, title, and code number of the old PD so it can be located. On every new PDD, the unique URLs, Titles, and code numbers both the rescind PDD and the new PDD should be clearly outlined so that all Americans for all history can locate electronically (and possibly in hard copy) each and every previous version of the PDD. Such an Executive Order should be retroactive back at least prior to January 2020, the start of the U.S. Epidemic of the World-wide Pandemic so that all aberrancies resultant from the previous practices will come to light—in short, the right of every American to transparency in their government's response to COVID-19 in accordance with our promise of Life and the Pursuit of Happiness.
- 2. Appropriate FDA and NIH physicians, DHHS and VHA governmental officials, and Editors of American Medical Journals who were involved in or know of this *de facto* cover-up should be required by the U.S. Congress to testify before the U.S. Congress and the American people regarding:
 - a. Overuse of Expanded Access (Compassion Use) which the FDA and the NIH were warned in 2015 not to utilize by the World Health Organization and the Institute of Medicine after it was employed in the Ebola outbreak.
 - b. Never-ending, prolonged-periods of drugs and biologics being continued as Investigational / Experimental designations under never-ending, continuing EUAs so that they are never available as officially-approved Drugs and Biologics to all of the general American public as organized therapeutically-appropriate treatments.
 - c. Disregard of the very definitions of Phase I, II, and III Clinical Trials that have resulted in inordinate delays or disparagement of textbook indications for such therapies as Passive Immunization.

- d. Rendering moot by bureaucratic flim-flam the Right to Try Act of 2018, PL-115-176.
- e. Reinstatement of all facets of the EMTALA of 1986 (PL-99-272) of which some provisions were suspended by former Secretary Azar on March 13, 2020 retroactive back to March 1, 2020. We are still under these rescinded EMTALA provisions and the entire basic guarantees of EMTALA have be violated and sullied:
 - 1. Stabilization of the Patient;
 - 2. Diagnosis of the Patient's disease to direct appropriate treatment;
 - and the appropriate Treatment and Disposition of the Individual.
 These have been *de facto* ignored in practice by some physicians and some hospitals throughout the U.S. over the last 18 months
- f. Corporate and Research conflicts-of-interest that resulted in the aforementioned disorganized, surpressed, and *de facto* negated EARLY immunotherapeutic treatment for all individuals should be proscribed.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S. Chief, Unit II General Surgery, St. Louis (SLU division) VAMC Professor, Department of Surgery, Saint Louis University School of Medicine

CC:

Anthony S. Fauci M.D.
Director, U.S. NIAID
U.S. National Institutes of Health
U.S. Department of Health & Human Services
5601 Fishers Lane, MSC. 9806
Bethesda, MD 20892-9806

Phone: 310-496-5717 FAX 301-402-3573

Re: Case #12276

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Acting Commissioner, U.S. Food and Drug Administration U.S. Department of Health & Human Services c/o CBER Ombudsman
Center for Biologics Evaluation and Research (CBER)
10903 New Hampshire Ave, W071-7240
Silver Springs, MD 20993-0002

Phone: 301-7906-8240

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14.0 2.0 2021-10-18 Dear Mr. President – Did USA Medicine abandon the People

150 Emerald Green Court St. Louis, MO. 63141 (314) 455-9482 (Pam's cell: 314-809-9634)

October 18, 2021

President Joseph Biden
President of the United States of America
The White House
1600 Pennsylvania Avenue
Washington, D.C.
202-456-1414

Re: NIH NIAID Case# 12276: On March 2, 2020 going forward, the FDA, the NIH, and *The White House* abandoned the USA Public by ignoring *Passive Immunization* (Convalescent Plasma or Sera [polyclonal antibodies—available since March 2020] and now Monoclonal Antibodies [cocktails of two monoclonal antibodies or single monoclonal antibodies—available since the Summer of 2020]), as an all-inclusive administration to everyone **EARLY**-in-the-course of COVID-19 viremia

Dear Mr. President:

Over the last 18 months I have tried to distill that which is important with regards to our therapeutically addressing the disease caused by coronavirus SARS-CoV-2. As a U.S. Government VA physician and surgeon with an official span of a quarter of a century in the Veterans Health Administration of the Department of Veterans Affairs, I, like all Federal Physicians, have had the responsibility to bring to your attention that which is most crucial in addressing this disease. For the last 18 months I have failed in my advocacy. In my own mind, I have hashed this out so many times that I don't know where even to begin. Since January 2020, the United States has been War—not with a foreign hostile nation—but against a chemically complex, non-sentient, hostile virus and, most of all, among ourselves. Maybe, what is most important, is that we should take from the past that which President Abraham Lincoln stated on March 4, 1865.:

"With malice toward none with charity for all with firmness in the right as God gives us to see the right let us strive on to finish the work we are in to bind up the nation's wounds, to care for him who shall have borne the battle and for his widow and his orphan ~ to do all which may achieve and cherish a just and lasting peace among ourselves and with all nations."

From the very beginning, we as a nation failed to promote and disseminate the distinction between <u>prevention with</u> *Active Immunization*: vaccination and <u>EARLY</u> treatment with *Passive Immunization*: (immunoglobulin therapies and antivirals like Remdesivir) and the inherent **synergism** between the two time-appropriate administrations. Along the way we demonstrated national hubris insulting with nations in their fight against COVID-19: e.g., calling it the "China virus." With my wife, we have raised five sons--so I can affirm that as a country, we acted like seventh-grade, grammar-school bullies. As the Spanish flu virus of 1918 probably originated on a chicken farm in the middle of Kansas, should not the Spanish Flu Pandemic of 1918 be referred to historically as the Kansas Flu Pandemic of 1918?

What follows in this cover letter is a documented timeline (620 entries) from prior to March 2020 to the present recorded for history of how we, the people of the United States of America, humanly both succeeded and failed: Medically, Scientifically, and Politically throughout the last 18 months. Throughout the last 18 months, all-too-often, we, as individuals, essentially have violated every commandment that Moses took down from the Mount. While there are many who individually have sacrificed all—including their lives--for the common good, we, as a nation, have been compelled to, all-to-often, do the wrong thing by advancing: personnel financial greed, narcissistic promotion, and morally reprehensible self-preservation and self-interest. Before God, we should ask as a nation for forgiveness for our short-sightedness: (1) from the world, (2) from our nation, (3) from our fellow man, and, most importantly, (4) from ourselves.

Imploring the grace of God, we should promote a call-to-arms of the application of the Golden Rule in the ongoing fight against COVID-19: *Do unto others as you would wish them to do unto you.* As President of the United States, you could promote not just vaccination--the prevention / diminution of the pathogenesis of coronavirus-CoV-2 by *Active Immunization*; but also a more-inclusive, coordinated, therapeutic effort of synergistic *Active Immunization* and *Passive Immunization*: EARLY treatment within 72 hours of contraction of COVID-19 symptomatology/diagnosis with *Passive Immunization* immunologic agents like Covid-19 convalescent plasma/sera and/or monoclonal antibodies and antivirals like Remdesivir for every man, woman, and child regardless of their vaccination status. As previously with the eradication of smallpox throughout the world in the 1970s, only with a synergistic, collective, therapeutic approach of coordinated massive vaccination; strict isolation, quarantine, and tracking; and treatment of the sick with EARLY administration of *Passive Immunization* and antivirals, will a successful conclusion to the coronavirus SARS-CoV-2 epidemic in the U.S.A. be forthcoming

On October 25, 2021, Dr. Fauci is slated to speak before the American College of Surgeons (ACS) Clinical Congress at which his session is being introduced by Julie A. Freischlag, MD, FACS, FRCSEd(Hon), DFSVS and Anthony Atala, M.D., F.A.C.S. Twenty years ago, Dr. Freischlag was the Chief of Surgery of the Milwaukee VAMC when I was the Chief of Surgery of the Edward Hines, Jr. VA of Maywood, IL. We shared many a moment of advocating for the betterment of the Veteran patients of VISN 12—sometimes to the annoyance of many in the VA including the VISN 12 Director at the time. With Dr. Freischlag's backing of Dr. Fauci's most-influential and most-opportune upcoming ACS speech, Dr. Fauci could definitively facilitate and promote an overall change in approach in this country to an organized, balanced (Active and Passive Immunization administration at appropriate times) therapeutic mindset in our fight against COVID-19.:

- 1. Vaccination (Active Immunization) of all men, women, and children in the U.S.A.
- 2. **EARLY Treatment** of all men, women, and children in the U.S.A. with COVID-19 Convalescent Plasma/Sera or Monoclonal Antibodies (*Passive Immunization*) and antivirals for infection and prophylaxis in high-exposure situations REGARDLESS OF VACCINATION STATUS.

- 3. Discontinuation of all the harmful, misleading rhetoric and discord that has distracted American Medicine and the people of the United States of America for the last 18 months.
- 4. (and probably, naïvely on my part) Promotion of a national sense of self-forgiveness possibly facilitated by a Presidential pardon of the entire nation regarding all our failings and short-comings in the fight against COVID-19.

Mr. President, thank you for considering this submission.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S. Professor, Department of Surgery, Saint Louis University School of Medicine Chief, Unit II (SLU) General Surgery, Surgical Service, John Cochran (St. Louis) VAMC

Cc: Anthony J. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, 5601 Fishers Lane, MSC. 9806, Bethesda, MD, 20892-9806. Phone 301-496-5717; FAX 301-402-3573. **For inclusion of the entire submission into NIAID file: Case #12276**

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16.0 3.0 2021-10-16 Patient states Government lied

150 Emerald Green Court St. Louis, MO. 63141 (314) 455-9482 (Pam's cell: 314-809-9634)

October 16, 2021

President Joseph Biden
President of the United States of America
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500
(202) 456-1414

Re: NIH NIAID Case# 12276: On March 2, 2020 going forward, the FDA, the NIH, and *The White House* abandoned the USA Public by ignoring *Passive Immunization* (Convalescent Plasma or Sera [polyclonal antibodies—available since March 2020] and now Monoclonal Antibodies [cocktails of two monoclonal antibodies or single monoclonal antibodies—available since the Summer of 2020]), as an all-inclusive administration to everyone **EARLY**-in-the-course of COVID-19 viremia

Dear Mr. President:

Several weeks ago, I phoned a Veteran patient that I have cared for in the past to discuss future follow-up in his care at the Saint Louis VAMC where I am an Attending General Surgeon. Much to my astonishment, the Veteran patient informed me that he did not want to present himself in person to the hospital for follow-up testing and on-going evaluation. When I asked him why, he stated he was not vaccinated against COVID-19--and he was not going to get vaccinated! When I asked him: "Why?"--he stated that the Federal Government had lied to us! I couldn't argue with his assertion—because he was and is correct. On October 25, 2021, I will be starting my 25th year as a federal physician/surgeon of the Veterans Health Administration, U.S. Department of Veterans Affairs, and I cannot deprecate that patient's assessment ---FOR IT IS CORRECT! As a federal physician/surgeon, this cover letter for all that follows is my federal-physician/surgeon duty to the people of the United States of America and to you, Mr. President, to attest to the insightful correctness of that Veteran patient's justification statement.

From March 2, 2020, when the physicians meeting with President Trump FAILED to define *Passive Immunization* in depth as the only viable, <u>EARLY treatment</u> of those infected with coronavirus SARS-CoV-2; in the <u>prophylaxis</u> of those at high risk of exposure to coronavirus SARS-CoV-2; and its <u>synergism</u> when used <u>EARLY</u> in the treatment of those having been administered *Active Immunization* (vaccination) who subsequently contract the disease, U.S. Medicine, U.S. Medical Research, and the U.S. Government have legitimated ongoing-unethical obfuscation and misinterpretive distractions; violations in the intentions of Federal law and policies; placebo coercion; rationing of *Passive Immunization* agents; and, most of all, <u>patient abandonment</u> that may have contributed to the deaths of over 700,000 Americans—not to mention the continued morbidities like pulmonary, cardiac, and renal failure in untold numbers of American COVID-19 survivors. In essence, our lack of definition and implementation of *Passive Immunization* for <u>ALL</u>-early-in-the-course-of-their-disease has led to the *de facto* withholding of *Passive Immunization* and has turned the fight against COVID-19 into a national

tragedy-of-withholding-EARLY-treatment akin to the Tuskegee Syphilis Experiment of the mid-20th Century.

Twenty-one years ago, former U.S. Surgeon General C. Everett Koop, M.D., F.A.C.S. addressed the American College of Surgeons Clinical Congress in San Francisco as the Keynote speaker. On October 25, 2021, Dr. Fauci will be the Keynote speaker presenting the Martin Memorial Lecture at the American College of Surgeons Clinical Congress entitled: *Lessons Learned and Remaining Challenges*. After reading Dr. Koop's speech of a quarter of a century ago and in Dr. Fauci's preparation for his upcoming lecture before the ACS Clinical Congress, he might read in-depth that which I have submitted to you and him today. What follows are portions previously submitted for historical preservation to the U.S. Copyright Office; a subsequent series of correspondence-not-yet submitted to the U.S. Copyright Office including this submission that I prepared/refined over the course of the last 18 months that have been and/or are now being submitted to you and Dr. Fauci's office for file NIH NIAID Case #12276. As I am the claimant of all my submissions to the U.S. Copyright Office, I authorize permission without any reservations, restrictions, or financial recompense, that anyone may reproduce any portion of my submissions as, I, as a Federal Physician and Surgeon, acknowledge and recognize that this is my duty to the United States of America.

U.S. Medicine and the U.S. Government have seemingly disregarded EARLY treatment with *Passive Immunization* which seems contrary to that which all physicians swear: *Primum non Nocere*. Have we forgotten the century-old admonition of Francis W. Peabody, M.D.: "...for the secret of the care of the patient is in caring for the patient"? It would seem that to move ahead and transform the present mindset in our country regarding *Passive Immunization*, we physicians and medical researchers should ask the understanding and forgiveness of the American people. While it is not our places to request your pardon as President of the United States of America, such a pardon like that of President Ford's pardon of President Nixon in 1974 over Watergate may interrupt this tragic path of denying EARLY treatment with *Passive Immunization* and its being complimentary with *Active Immunization* (vaccination) efforts. As I have worked for the Veterans Health Administration for a quarter of a century and have advocated for the Veteran Patient, in the coming days, Mr. President, the last sentence of President Lincoln's second inaugural address³ seems most apropro:

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan—to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

Thank you for this consideration.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.
Professor, Department of Surgery, Saint Louis University School of Medicine
Chief, Unit II (SLU) General Surgery Division, Surgical Service, John Cochran (St. Louis) VAMC

Cc: Anthony J. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, 5601 Fishers Lane, MSC. 9806, Bethesda, MD, 20892-9806. Phone 301-496-5717; FAX 301-402-3573. **Re: Case #12276**

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17.0 4.0 2021-10-02 What Would C. Everett Koop, M.D., F.A.C.S. Say?

Dear Mr. President:

For the last 18 months I have attempted to communicate with the commissioner of the FDA; the Director of the NIAID, (NIH NIAID Case #12276); and *The White House*. As a general surgeon for 40 years, I have been inculcated in treating each person individually pulling-out-all-the-stops to provide treatment with the goal of diminished morbidity and improving survival of each individual presenting with a life-threatening malady. The universal mindset of a general surgeon is epitomized for me by my former mentor, J. Eugene Lewis, M.D., F.A.C.S., who like C. Everett Koop, M.D., F.A.C.S., trained in the 1940s under one of the most significant founders of Pediatric Surgery, Robert Gross, M.D., F.A.C.S. As was written of Dr. Koop in his NIH biography, the politicians in 1982 were worried about his confirmation as Surgeon General because of his past General Surgery clinical experience focusing and caring for the individual patient which seemed a contradictory deficiency to the Surgeon General's role of caring for the well-being of our nation in the collective. Dr. Koop's leadership with the mindset of the importance of treating each individual patient has confirmed him for history as the greatest Surgeon General of our time demonstrating his adherence to the intent of the American College of Surgeons Fellowship Pledge (part of version 1986):
...Moreover, I promise to deal with each patient as I would wish to be dealt with were I in his position...
https://www.facs.org/about-acs/archives/pasthighlights/pledge

From March 2, 2020, to the present, the USA collectively abandoned patients infected with COVID-19 by rejecting **EARLY TREATMENT** of each infected individual patient with PASSIVE IMMUNIZATION: e.g., COVID-19 convalescent plasma, COVID-19 convalescent serum, or monoclonal antibodies/cocktails (which today are still investigational / experimental after greater than a million doses administered in the U.S.A.; sold in foreign countries to those that can pay; and are being rationed due to lack of availability in the U.S.A. at present.) As a general surgeon for 40 years, I have always pulled out all-the-stops for every patient figuratively throwing in the "kitchen sink" for every trauma patient EARLY in their treatment during the "Golden Hour" with one goal in mind—the survival of the individual patient. SHAME ON US as U.S. Medicine for withholding EARLY PASSIVE IMMUNITY TREATMENTS from every individual who contracted COVID-19 (both unvaccinated and vaccinated) because the politicians, businessmen, and research scientists had major conflicts of interest with regards to:

- (1) promotion of synthetic forms of passive immunization treatment preferentially to COVID-19 Convalescent Plasma by distracting and dismissing from the American consciousness the most available Passive Immunization agent, COVID-19 Convalescent Plasma (CCP) (\$200 a dose of 200 ml of FFP) versus monoclonal antibody cocktails (~\$3000 a dose with limited availability at present) for the last 18 months;
- (2) fostering corporate and personal wealth by denigrating CONVALESCENT PLASMA--THE ORIGINAL FORM of the 120 year old Noble prize-winning

EARLY treatment of a virus with PASSIVE IMMUNIZATION--by administration not within 72 hours of diagnosis when all such agents are administered but when it is less effective late-in-the-disease when the cytokine cascade^{401,459,486} and the bradykinin storm^{90,258,307,459,486} are most prominent and the individual is potentially at deaths-door (age-stratified mortality-rates defined by derived equations from CDC database):

(a)
$$0-45$$
 years: $y = 0.0008x - 0.0103$, $R^2 = 0.825$ and (b) 46 years - >85 years: $y = 0.0049x - 0.1216$ $R^2 = 0.997$;

- (3) by rejecting established FDA/NIH research directives and policies by:
 - (a) the FDA publishing research-proscribed data generated from Expanded Access (compassionate use) programs like the Mayo Clinic/FDA Expanded Access program,
 - (b) subjecting this country to a series of underpowered, non-age-stratified, prospective placebo-controlled studies of CCP given at the WRONG TIME with the majority of 722,000 units administered,
 - (c) abrogating the intent of PL-115-176, the Right to Try Act, and PL-99-272 EMTALA, and
 - (d) continuing all COVID-19 PASSIVE IMMUNITY agents as Investigational (Experimental) with no-end-in-sight EUAs when CCP and monoclonal antibodies are all Passive Immunity agents which are <u>all</u> biosimilar to <u>FDA approved Passive Immunologic agents</u> like rabies vaccine, Rhogam, hyperimmune tetanus globulin, IVIG, vaccinia immune gamma-globulin, the RSV monoclonal cocktail, etc.

Mr. President, unfortunately, the present societal mindset of most vaccinations is based on past personal experience. As children and young adults, you and I received the Salk vaccine (a killed polio virus) and in 1960 also received the oral Sabin vaccine (a live attenuated polio virus) on sugar cubes on three Sundays (month 0, month 2, and month 6). The provision of a killed-virus or live-attenuated-virus were to stimulate in the vaccinated individual both polyclonal immunoglobulins and cellular-mediated immunity.

Not directed against the whole virus, the present IM vaccines of Pfizer and Medina are directed at the mRNA pathway to stimulate an IgG immunoglobulin serologic line against one specific coded segment of spike protein. SARS-Cov-2 coronavirus is contracted through the nasopharynx which is protected by IgA. Experimentally, the IgA serologic five-day response to a recombinant SARS-CoV-2 nucleocapsid is 92.7%. The theory of herd immunity is based on 70% of the herd contracting the virus (by individual infection or by immunization with a killed or live-attenuated whole virus vaccine)—not a monoclonal antibody generating vaccine.

The present mindset using only *Active Immunization* in stopping the American COVID-19 epidemic is flawed. After two centuries of the world failing in the elimination of smallpox using *Active Immunization* only with William Jenner's cowpox vaccine in the treatment of smallpox, the World Health Organization eradicated smallpox (1970s) throughout the world by vaccinating as many unvaccinated as possible; tracking and isolating new cases and treating with convalescent plasma (*Passive Immunization*); and treating individual high exposure contacts with *Passive Immunization* and vaccinating. In short, *Active* and *Passive Immunization* are distinct in treatment indications and synergistic in application.

Mr. President, we, as a nation, need to both treat immediately <u>all</u> those who contract COVID-19 (both unvaccinated and vaccinated) with early *Passive Immunization* (monoclonal antibodies and convalescent sera / plasma) and maximally work to vaccinate *Active Immunization* the unvaccinated as is the present exclusively unilateral national implementation plan. You need the advice of the experts unencumbered by the intimidation of the previous administration. In short, you and the nation need a lesson Clinical Immunology 101. Most of all, we as Federal Physicians and U.S. Medicine need to acknowledge our shortcomings and forgive ourselves. You need the best and the brightest to advise you. While presumptuous on my part, might I suggest the following to be some who could make-up such an uninhibited advisory council if the intimidation of the prior administration was proscribed:

Francis S. Collins, M.D.; Anthony Fauci, M.D.; Rochelle Walensky, M.D.; Vivek Murthy, M.D.; Stephen Hahn, M.D., Janet Woodcock, M.D.; Debroah Birx, M.D.; Peter Marks, M.D.; RADM Denise M. Hinton, RN, MS; Michael Joyner, M.D.; Arturo Casadevall, M.D.; Liise-anne Pirofski, M.D.; Jay Epstein, M.D.; Louis M. Katz, M.D.; Leonard Schleifer, M.D.; George Yancopoulos, M.D.; Eric J. Rubin, M.D.; Philip Drazen, M.D.; Howard Bauchner, M.D.; Catherine D. DeAngelis, M.D.; Jeffrey P. Henderson, M.D.; Bruce Hall, M.D., F.A.C.S.; Colonel Jeffrey A. Bailey, M.D., F.A.C.S., USAF; Steven L. Liebman, M.D. (Acting Under Secretary, VHA of DVA); Richard Stone, M.D.; as a legal counsel representative: Jeffrey Rosen, J.D. (former acting Attorney General from December 23, 2020 to January 20, 2021, who saved this nation much like Edmund G. Ross 150 years ago); representatives from the Association of American Blood Banks (AABB) and the American Red Cross; Dawn O'Connell, J.D., FDA Assistant Secretary for Preparedness and Response, DHHS; etc.

Mr. President, the nation needs HOPE. Like President Ford in 1974, this country needs a pardon that will promote a refocusing and renewal of our fight with COVID-19 as we have promised in our Constitution as a preamble:

We, the people of the United States, Order to form a more perfect Union, establish Justice, insure domestic Tranquility, provide for the common defense, **promote the general Welfare**, and secure the Blessings of Liberty to ourselves and our Posterity, do ordain and establish this Constitution for the United States of America.

Twenty years ago, the Institute of Medicine released the book: *To Err is Human: Building a Safer Health System*. Subsequently, Ms Goldstein of the Joseph and Rose Kennedy BioEthics Library of Georgetown University requested for the Library's permanent published files the article: Andrus CH, Villasenor EG, Kettelle JB, Roth R, Sweeney AM, Matolo NM: "To Err is

Human": Uniformly reporting medical errors and near misses, a naïve, costly, and misdirected goal in which we analyzed governmental error reporting systems in the VA. We concluded:

Error-reporting should not be our goal, but only a means of learning from our short-comings to help improve the future care of our patients. As Francis W Peabody, MD, told the students of the Harvard Medical School more than 70 years ago: "...the secret of the care of the patient is in caring for the patient."

Going forward, we should pray for God's forgiveness for our short-sightedness in the medical fight against COVID-19 and then, as physicians, reaffirm individually to *Primum non Nocere*—for that is our oath; and, as a nation, recommit collectively to: ...promote the General Welfare...!

Respectfully,

Charles H. Andrus, M.D., F.A.C.S. Chief, Unit II (SLU) General Surgery Division, Surgical Service, St. Louis VAMC Professor, Department of Surgery, Saint Louis University School of Medicine

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18.0 5.0 2021-09-19: THE TRAGIC METHOLOGY OF ELECTRONIC OVERWRITING OF OFFICIAL GOVERNMENT DOCUMENTS <u>IS AN OBSTRUCTION OF JUSTICE</u>

Dear Mr. President:

Please forgive my forwardness of this cover letter of the documentation I will be presenting to you. Over the last 18 months I have submitted documentation with the U.S. Department of Health and Human Services through the office of the NIAID of the National Institutes of Health, the Office of the Commissioner of the FDA, and many other federal offices including the Office of the President of the United States with little response to my advocacy. As a federal physician of 24 years of service in the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs, it is my duty to bring to your attention that which has collectively been detrimental to the people of the United States of America. While my past focus has been to promote *Passive Immunization* methodologies in the early treatment (<72 hours from diagnosis) of COVID-19 (e.g.: Convalescent Plasma, Convalescent Sera, Monoclonal Antibodies, and Monoclonal Antibody cocktails), the most glaring foundational problem common to our addressing the conoravirus SARS-CoV-2 has been harmful selective transparency, misdirection, obfuscation, and lies promoted by U.S. Medicine, U.S. Medical Research, U.S. Pharma, and agencies of the Executive Branch of the Federal Government (e.g.: FDA, NIAID, NIH, CDC, USPHS, VHA of the DVA, etc.). By (1) altering their adherence to their own-stated policies and directives; (2) violating or negating public laws: e.g.: EMTALA, PL-89-97 and The Right to Try Act, PL-115-176; and (3) misinterpreting fundamental immunology concepts; (4) misapplying and ignoring research ethics as proclaimed by the Nuremberg Code, the Helsinki Accords, and the Belmont Report; (5) redefining incorrectly key medical terminology, and (6) misrepresenting the very definitions promoted by the U.S. Department of Health and Human Services: e.g.: Clinical Trials, placebos, EUA, Expanded Access, and the very foundational Congressionally-mandated decrees establishing the FDA (over a century ago), U.S. Medicine and the U.S. Government have synergistically failed the American people!

Attached to this cover letter are multiple aspects of where we, as the U.S.A. in the fight against COVID-19 went wrong. Below is the latest personal example that was presented to my family by my wife purchasing two of the at-home COVID-19 Antigen Self tests: Abbott's BinaxNOW and Quidel's QuickVue. Both contain the following statement (with slight variations):

This product has not been FDA cleared or approved, but has been authorized by the FDA under an Emergency Use Authorization (EUA) for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens...

Except for Remdesivir (VELKURY, NDA #214787, October 22, 2020) and Pfizer's COVID-19 vaccine (COMIRNATY, BL 125742/0, August 23, 2021), all other agents being utilized in the fight of COVID-19 for testing, treatment, and prevention of COVID-19 are under Emergency Use Authorizations (EUAs) which mean they are <u>all</u> "Investigational" or in Medical Research terminology: Experimental. We, as a nation, have given out over 200 million doses of vaccines (Active Immunization) under the auspices of Medical Research experimentation during this pandemic.—It is no wonder that a large percentage of the American people still refuse to be vaccinated with these "Experimentational Agents." The generic term Passive Immunization (Convalescent plasma/sera and monoclonal antibodies) has never been mentioned to the American public even though ~722,000 units of COVID-19 convalescent plasma/sera have been administered over the last 18 months AT THE WRONG TIME late in the course of the disease!

Normally, in NIH authorized Clinical Trials and in policies of the FDA, successful completion of a phase 1 trial with regards to <u>safety</u> is met when approximately 20 – 40 individuals with the disease have had minimal side-effects attributable to the Investigational agent when administered. When efficacy has been demonstrated in Phase 2/3 studies (200-400 individuals) then an agent usually receives FDA approval as a new drug or biologic. Over the last 18 months, hundreds of thousands of these agents of Active and Passive Immunization have been given out by hospitals, infusion centers, and other emergency sites under the auspices of EUAs—Experimental Administrations.

While someone purchasing the OTC tests mentioned above assumes they are <u>screening tests</u> for SARS-CoV-2 antigens in the nares of an individual, **neither meets medical sensitivity significance criteria** for a screening test of 2 standard deviations from the mean (a 95% confidence level): Abbott's BinaxNOW 91.7% sensitivity and Quidel QuickVue At-Home OTC COVID-19 Test of 83.5% sensitivity. **Most of all Mr. President**, while both tests within their packaged directions states that the reagents of the test can be harmful if contacted by an individual, NO WHERE is it stated the legal FDA warning of: KEEP OUT OF REACH OF CHILDREN (21 CFR 369.9) on the packaging. I chose this example because it presents minor lapses of dereliction to duty by the FDA when overall there have been major infractions by the FDA and the NIH.

Throughout the last 18 months, both the FDA and NIH have disregarded or conveniently overlooked the intent, if not the letter-of-the-law, regarding generic adherence and protection of patients' rights (and more specifically, they ignored PL-115-176, The Right to Try Act at every turn) which, in some circumstances, may have been illegal but, in all instances, violated the collective trust of the American people. <u>Collectively, shame on U.S. Medicine and shame on the agencies of the U.S. Department of Health and Human Services!</u> They should all apologize to the U.S. people!

Mr. President: As Dr. Fauci, you, and I grew up in the era of the Roman Catholic Latin Mass, we of U.S. Medicine and the Executive Branch of the U.S. Government should all be beating our breasts and stating: Mea Culpa, Mea Culpa, Mea Maxima Culpa. In the attached documentation, I will try to explain the following:

- 1. My summarization of the natural course of the disease of COVID-19 caused by the coronavirus SARS-CoV-2 including:
 - a. The size of the coronavirus SARS-CoV-2 (50 140 nm) and its implications regarding N95 masks (there are no true antiviral masks and N95 masks inhibit 95% of particles less than 300 nm in size). https://blogs.cdc.gov/niosh-science-blog/2009/10/14/n95/ and https://www.news-medical.net/health/The-Size-of-SARS-CoV-2-Compared-to-Other-Things.aspx
 - b. The implications of the longitudinal graphs of daily new cases of COVID-19 and daily deaths attributable to COVID-19. https://ourworldindata.org/coronavirus Mr. President, did you know that the graphs of the decline of new cases and new deaths represent logarithmic decays that approach zero daily cases and deaths asymptotically?
 - c. As we have <u>not</u> until this summer officially treated early (before the cytokine cascade and the bradykinin storm late phase) COVID-19 with passive immunization (monoclonal antibodies), one can mathematically define the natural untreated death rate of COVID-19 patients. The derived equations and graphs from the CDC weekly reports regarding mortality by age groups are the following https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge:

$$0-45 \text{ years}$$
 $y = 0.0008x - 0.0103 \text{ R}^2 = 0.8254$
 $46 - > 85 \text{ years}$ $y = 0.0049x - 0.1216 \text{ R}^2 = 0.9972$

From 4/2020 to present:

•	., = 0 = 0 to pro.	J	
	Age Range	Mortality %	Deaths by Age Group
		Infected	100,000 in that Age Group
	0 - 17 yrs	0.05%	50 / 100,000
	18 - 29 yrs	0.41%	410 / 100,000
	30 - 39 yrs	1.19%	1,190 / 100,000
	40 - 49 yrs	3.10%	3,100 / 100,000
	50 - 64 yrs	15.47%	15,470 / 100,000
	65 - 74 yrs	21.63%	21,630 / 100,000
	75 - 84 yrs	27.06%	27,060 / 100,000
	\geq 85 yrs	31.09%	31,090 / 100,000

- 2. The chronology of what went wrong in the implementation of Passive Immunization from January 2020 to the present.
- 3. It would be my suggestion along with your present COVID-19 White House Task Force members, you might invite to the White House for an educational informational session for you the following physicians and present and former governmental individuals:
 - Francis S. Collins, M.D.; Anthony Fauci, M.D.; Stephen Hahn, M.D.; Janet Woodcock, M.D., Debroah Birx, M.D.; Peter Marx, M.D.; RADM Denise M. Hinton, RN, MS;

Michael Joyner, M.D.; Arturo Casadevall, M.D.; Liise-anne Pirofski, M.D.; Jay Epstein, M.D.; Louis M. Katz, M.D.; Leonard Schleifer, M.D.; George Yancopoulos, M.D.; Eric J. Rubin, M.D.; Philip Drazen, M.D.; Howard Bauchner, M.D.; Catherine D. DeAngelis, M.D.; Jeffrey P. Henderson, M.D.; Bruce Hall, M.D.; Steven L Liebman, M.D., Richard Stone, M.D. as a legal counsel representative: Jeffrey Rosen, J.D. (former acting Attorney General from December 23, 2020 to January 20, 2021.); representatives from the Association of American Blood Banks (AABB) and the American Red Cross, Dawn O'Connell, J.D., Assistant Secretary for Preparedness and Response, DHHS; etc.

- 4. What could be on the agenda for such a meeting:
 - a. A short course in Clinical Immunology regarding the differences between Active and Passive Immunization presented to the President of the United States and how these agents should be utilized synergistically to end the COVID-19 epidemic in the U.S.A.
 - b. Discussion of how to educate the America public and organize infusion centers around the nation for the EARLY administration of Passive Immunization (Convalescent Plasma, Convalescent Sera, Monoclonal Antibodies, and Monoclonal Antibody Cocktails) and Antiviral agents like Remdesivir. Discussion on how to provide the early administration of Passive Immunization throughout the country. Discuss how to mobilized the nation's blood bank to collect and distribute large quantities of COVID-19 convalescent plasma Fresh Frozen plasma (FFP) as was done during WWII administered initially administrated by Charles Drew, M.D., FACS and the by Eleanor Roosevelt. (Today, in one week, literally with 20 donations daily of COVID-19 Convalescent Plasma (CCP) to the >5000 blood banks throughout the U.S.A., 700,000 units of convalescent FFP can be generated. As there are two doses of 200 ml of "high dose" CCP per FFP unit, 1.4 million units per week are possible. If the FFP is "low dose", doubling the volume to a full unit of FFP (400 ml) will double the polyclonal antibodies administered to an individual (e.g.: 2 or 3 x low dose = one high dose unit of CCP) Most of all, on August 23, 2020 using data from approximately 94,000 units administered late in the disease (the wrong time) by the Mayo Clinic/FDA Expanded Access program (compassionate use of which the data should not have been used) the FDA still concluded that "high dose" was better that "low dose" CCP. Mr. President, would it not seem reasonable that "high dose" is better than NO DOSE!
 - c. Mr. President, with the mortality calculations regarding children under the age of 12 derivable from 1c above, **should a school holiday be declared until such time as all the children can be vaccinated?** Right now we are essentially putting our unvaccinated children who have not contracted previously COVID-19—thus, being individually immunity naïve to COVID-19--in harms way.

Using the equation: y = 0.0008x - 0.0103 R²=0.8254

One can calculate the estimated mortality by year per 100,000/infected. (But by the least square fit equation derived from the CDC data of 0-45 years, the predicted age range mortalities really predicts finite mortality from age 13 years and above)

Age	Mortality %	Deaths by Age Group
	Infected	100,000 in that Age Group
4 yrs	-0.71%	0
5 yrs	-0.63%	0
6 yrs	-0.55%	0
7 yrs	-0.47%	0
8 yrs	-0.39%	0
9 yrs	-0.31%	0
10 yrs	-0.23%	0
11 yrs	-0.15%	0
12 yrs	-0.07%	0
12	0.010/	10
13 yrs	0.01%	10
14 yrs	0.09%	90
15 yrs	0.17%	170
16 yrs	0.25%	250
17 yrs	0.33%	330
18 yrs	0.41%	410
19 yrs	0.49%	490

d. Discussion of the endpoints regarding full approval of all the agents under EUAs that have demonstrated efficacy by appropriate studies (NOT CCP GIVEN LATE IN THE DISEASE AND LACKING AGE STRATIFIED). The FDA can designate as full-fledged drugs and biologics in the treatment of COVID-19 all the present Passive and Active Immunization agents being utilized by shear numbers of administrations of these agents over the last 18 months when they were give early (<72 hours after diagnosis) and when analyzed by age-stratification!

Mr. President, by now you are probably wondering how we got into this mess. Well, frankly, it was a lot of little errors or presentations of selective transparency that cascaded in misleading and misdirecting U.S. Medicine and the US government.

1. The worst error was constructing administration criteria for CCP and Remdesivir at "deaths-door" rather than within 72 hours of diagnosis. On March 24, 2020, the following FDA announcement based on a misinterpretation of a February 2020 Chinese epidemiology paper published in JAMA which never speaks of treatment of COVID-19 was issued that set into motion administration of CCP at the WRONG TIME, initiated a multitude of NIH clinical trials based on the WRONG TIME, and initiate Clinical Practices of administration of CCP at the WRONG TIME that even now have not been rescinded in practice!:

Investigational COVID-19 Convalescent Plasma - Emergency INDs

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March 24, 2020

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from public health threats including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to doing everything we can to provide timely response efforts to this pandemic and facilitate access to investigational drugs for use in patients with serious or immediately life-threatening COVID-19 infections.

One investigational treatment being explored for COVID-19 involves the use of convalescent plasma collected from recovered COVID-19 patients. It is possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. Although promising, convalescent plasma has not been shown to be effective in every disease studied. It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so. Investigators wishing to study the use of convalescent plasma are encouraged to submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).

Although participation in clinical trials is one way for patients to obtain access to convalescent plasma, these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the expanding COVID-19 outbreak presents, while clinical trials are being conducted, FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency Investigational New Drug Applications (eINDs) for Individual patients under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This does not include the use of COVID-19 convalescent plasma for the prevention of infection.

Healthcare providers interested in the emergency use of investigational COVID-19 convalescent plasma under a single patient emergency IND should consider the following:

COVID 19 Convalescent Plasma

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Additional considerations for donor eligibility should be addressed, as follows:

- · Prior diagnosis of COVID-19 documented by a laboratory test
- · Complete resolution of symptoms at least 14 days prior to donation
- · Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic
 test from blood. A partial list of available tests can be accessed at <a href="https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices/emergency-use-authorizations-medical-devices/emergency-use-authorizations-
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug-Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

- . Eligible patients for use under expanded access provisions:
 - Must have laboratory confirmed COVID-19
 - Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or
 - multiple organ dysfunction or failure
 - Must provide informed consent

How to obtain authorization for use of COVID-19 convalescent plasma

- For request that are not highly time sensitive (response from FDA provided within 4 to 8 hours), the requesting
 physician may contact FDA by completing form 3926 (https://www.fda.gov/media/98616/download) and submitting the
 form by email to Covid-19@FDA.HHS.gov.
 - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements of 21 CFR 312.305 and 312.310.
 - The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
 - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.
 - FDA will review the request and, upon approval, FDA will send the requesting physician a confirmatory email that includes the emergency IND number.
- In the event of an emergency that is highly time sensitive (response required in less than 4 hours) or where the
 provider is unable to complete and submit form 3926 due to extenuating circumstances, the provider may contact
 FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
 - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 15 working days of FDA's authorization of the use.

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

[^]1Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72†[^]314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Content current as of: 03/24/2020

A British Medical Journal article: https://www.bmj.com/content/bmj/368/bmj.m1256.full.pdf of March 26, 2020 documented for the world this announcement with it attached three references:

- 1 FDA. Investigational covid-19 convalescent plasma—emergency INDs.

 https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber-investigational-covid-19-convalescent-plasma-emergency-inds (When one attempts to use the Wayback machine to find this site, the response is Wayback Machine has not archived that URL.)
- Hixenbaugh M. FDA will allow doctors to treat critically ill coronavirus patients with flood from survivors. NBC News 2020 Mar 24.

 www.nbcnews.com/news/us-news.com/news/us-news/fda-will-allow-doctors-treat-critically-ill-coronavirus-patients-blood-n1167831 which contains the hyperlink: emergency protocols approved by the FDA which directs to: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma (the February 11, 2021 which is the Wayback Machine first "captured". ****Need to research this more as previous with the Wayback Machine pointed to April 8, 2020)
- Palca J. FDA expedites treatment of seriously ill covid-19 patients with experimental plasma. National Public Radio, 24 Mar 2020.

 www.npr.org/sections/coronavirus-live-updates/2020/03/24/820939536/fda-expedite-treatment-of-seriously-ill-covid-19-patients-with-experimental-plasma which contains the hyperlink: emergency protocols approved by the FDA which directs to: www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma (the February 11, 2021 which is the Wayback Machine first "captured". ****Need to research this more as previous with the Wayback Machine pointed to April 8, 2020)

Reference 1 points to a URL that no longer exists and the other two in the body of the article points to the URL: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drugapplications-inds-cber-regulated-products/recommendations-investigational-covid-19convalescent-plasma of February 11, 2021. Previously, if one copied to this URL into the Wayback Machine of the Internet Archive, the initial document in April 2020 which was an expost facto document of April 8, 2020. This represents the now missing "reference "1" regarding justification for the criteria incorrectly attributed to the JAMA article of Wu Z, McGoonan JM...(see above)" of the FDA March 24, 2020 announcement. The Incorrect "Eligibility Criteria" criteria was the limiting factor regarding administration of CCP and Remdesivir until September 2, 2020 and August 28, 2020, respectively. The FDA was so "quiet" about these corrections that the VHA issued in November 2020 administration inclusion regarding Remdesivir which was (under the drug name VELKURY) as October 22, 2020 the only FDA fully-approved antiviral (NDA #214787) in the (early) treatment of COVID-19. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf THE WRONG ADMINISTRATION INCLUSION CRITERIA remains the official criteria of the VHA listed on the internet to this day.

https://vanf.app/CFU PDF/Remdesivir VEKLURY November2020.pdf

2. Mr. President, would you consider an Executive Order banning the present practice across the Executive Branch of the U.S. Government of "Overwriting" official documents without official designation of the document(s) rescinded? You could then direct in the Executive Order the reinstatement of the practice that all official documents, policies, directives, and memos of all Departments of the Executive Branch of the U.S. Government document on the face sheet list the previously rescinded document, policy, directive, and/or memo on the present version that it was replacing.—that would be TRUE GOVERNMENTAL TRANSPARENCY. At present, if the replacement document is overwritten electronically and the exact URL is maintained, the replaced/rescinded document can ONLY be located, if the URL has not been changed, by pasting the existing URL into the "Wayback Machine" of the Internet Archive (300 Funston Avenue, San Francisco, CA, 94118, 415-561-6767). This can only occur if the Internet Archive is fortunate to have captured a digital version of the previously overwritten document!

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19.0 6.0 2021-10-19. How Did We Get Into This Mess?

Dear Mr. President:

Please forgive my forwardness of this cover letter of the documentation I will be presenting to you. Over the last 18 months I have submitted documentation with the U.S. Department of Health and Human Services through the office of the NIAID of the National Institutes of Health, the Office of the Commissioner of the FDA, and many other federal offices including the Office of the President of the United States with little response to my advocacy. As a federal physician of 24 years of service in the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs, it is my duty to bring to your attention that which has collectively been detrimental to the people of the United States of America. While my past focus has been to promote *Passive Immunization* methodologies in the early treatment (<72 hours from diagnosis) of COVID-19 (e.g.: Convalescent Plasma, Convalescent Sera, Monoclonal Antibodies, and Monoclonal Antibody cocktails), the most glaring foundational problem common to our addressing the conoravirus SARS-CoV-2 has been harmful selective transparency. misdirection, **obfuscation**, and lies promoted by U.S. Medicine, U.S. Medical Research, U.S. Pharma, and agencies of the Executive Branch of the Federal Government (e.g.: FDA, NIAID, NIH, CDC, USPHS, VHA of the DVA, etc.). By (1) altering their adherence to their own-stated policies and directives; (2) violating or negating public laws: e.g.: EMTALA, PL-89-97 and The Right to Try Act, PL-115-176; and (3) misinterpreting fundamental immunology concepts; (4) misapplying and ignoring research ethics as proclaimed by the Nuremberg Code, the Helsinki Accords, and the Belmont Report; (5) redefining incorrectly key medical terminology, and (6) misrepresenting the very definitions promoted by the U.S. Department of Health and Human Services: e.g.: Clinical Trials, placebos, EUA, Expanded Access, and the very foundational Congressionally-mandated decrees establishing the FDA (over a century ago), U.S. Medicine and the U.S. Government have synergistically failed the American people!

Attached to this cover letter are multiple aspects of where we, as the U.S.A. in the fight against COVID-19 went wrong. Below is the latest personal example that was presented to my family by my wife purchasing two of the at-home COVID-19 Antigen Self tests: Abbott's BinaxNOW and Quidel's QuickVue. Both contain the following statement (with slight variations):

This product has not been FDA cleared or approved, but has been authorized by the FDA under an Emergency Use Authorization (EUA) for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens...

Except for Remdesivir (VELKURY, NDA #214787, October 22, 2020) and Pfizer's COVID-19 vaccine (COMIRNATY, BL 125742/0, August 23, 2021), all other agents being utilized in the fight of COVID-19 for testing, treatment, and prevention of COVID-19 are under Emergency Use Authorizations (EUAs) which mean they are <u>all</u> "*Investigational*" or in Medical Research

terminology: **Experimental**. We, as a nation, have given out almost 200 million doses of vaccines (**Active Immunization**) under the auspices of **Medical Research experimentation** during this pandemic.—It is no wonder that a large percentage of the American people still refuse to be vaccinated with these "Experimentational Agents." The generic term **Passive Immunization** (Convalescent plasma/sera and monoclonal antibodies) has never been mentioned to the American public even though ~722,000 units of COVID-19 convalescent plasma/sera have been administered over the last 18 months **AT THE WRONG TIME late in the course of the disease!**

Normally, in NIH authorized Clinical Trials and in policies of the FDA, successful completion of a phase 1 trial with regards to <u>safety</u> is met when approximately 20-40 individuals with the disease have had minimal side-effects attributable to the Investigational agent when administered. When efficacy has been demonstrated in Phase 2/3 studies (200-400 individuals) then an agent usually receives FDA approval as a new drug or biologic. Over the last 18 months, hundreds of thousands of these agents of Active and Passive Immunization have been given out by hospitals, infusion centers, and other emergency sites under the auspices of EUAs—Experimental Administrations.

While someone purchasing the OTC tests mentioned above assumes they are <u>screening tests</u> for SARS-CoV-2 antigens in the nares of an individual, **neither meets medical sensitivity significance criteria** for a screening test of 2 standard deviations from the mean (a 95% confidence level): Abbott's BinaxNOW 91.7% sensitivity and Quidel QuickVue At-Home OTC COVID-19 Test of 83.5% sensitivity. **Most of all Mr. President**, while both tests within their packaged directions states that the reagents of the test can be harmful if contacted by an individual, NO WHERE is it stated the legal FDA warning of: KEEP OUT OF REACH OF CHILDREN (21 CFR 369.9) on the packaging. I chose this example because it presents minor lapses of dereliction to duty by the FDA when overall there have been major infractions by the FDA and the NIH.

Throughout the last 18 months, both the FDA and NIH have disregarded or conveniently overlooked the intent, if not the letter-of-the-law, regarding generic adherence and protection of patients' rights (and more specifically, they ignored PL-115-176, The Right to Try Act at every turn) which, in some circumstances, may have been illegal but, in all instances, violated the collective trust of the American people. Collectively, shame on U.S. Medicine and shame on the agencies of the U.S. Department of Health and Human Services! They should all apologize to the U.S. people!

Mr. President: As Dr. Fauci, you, and I grew up in the era of the Roman Catholic Latin Mass, we of U.S. Medicine and the Executive Branch of the U.S. Government should all be beating our breasts and stating: Mea Culpa, Mea Culpa, Mea Maxima Culpa. In the attached documentation, I will try to explain the following:

- 1. My summarization of the natural course of the disease of COVID-19 caused by the coronavirus SARS-CoV-2 including:
 - a. The size of the coronavirus SARS-CoV-2 (50 140 nm) and its implications regarding N95 masks (there are no true antiviral masks and N95 masks inhibit

95% of particles less than 300 nm in size). https://blogs.cdc.gov/niosh-science-blog/2009/10/14/n95/ and https://blogs.cdc.gov/niosh-science-blog/2009/10/14/n95/ and https://www.news-medical.net/health/The-Size-of-SARS-CoV-2-Compared-to-Other-Things.aspx

- b. The implications of the longitudinal graphs of daily new cases of COVID-19 and daily deaths attributable to COVID-19. https://ourworldindata.org/coronavirus Mr. President, did you know that the graphs of the decline of new cases and new deaths represent logarithmic decays that approach zero daily cases and deaths asymptotically?
- c. As we have <u>not</u> until this summer officially treated early (before the cytokine cascade and the bradykinin storm late phase) COVID-19 with passive immunization (monoclonal antibodies), one can mathematically define the natural untreated death rate of COVID-19 patients. The derived equations and graphs from the CDC weekly reports regarding mortality by age groups are the following https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge :

$$0-45 \text{ years}$$
 $y = 0.0008x - 0.0103 \text{ R}^2 = 0.8254$
 $46 - > 85 \text{ years}$ $y = 0.0049x - 0.1216 \text{ R}^2 = 0.9972$

From 4/2020 to present:

Age Range	Mortality %	Deaths by Age Group
	Infected	100,000 in that Age Group
0 - 17 yrs	0.05%	50
18 - 29 yrs	0.41%	410
30 - 39 yrs	1.19%	1190
40 - 49 yrs	3.10%	3100
50 - 64 yrs	15.47%	15470
65 - 74 yrs	21.63%	21630
75 - 84 yrs	27.06%	27060
≥ 85 yrs	31.09%	31090

- 2. The chronology of what went wrong in the implementation of Passive Immunization from January 2020 to the present.
- 3. It would be my suggestion along with your present COVID-19 White House Task Force members, you might invite to the White House for an educational informational session for you the following physicians and present and former governmental individuals:
 - Francis S. Collins, M.D.; Anthony Fauci, M.D.; Stephen Hahn, M.D.; Janet Woodcock, M.D., Debroah Birx, M.D.; Peter Marx, M.D.; RADM Denise M. Hinton, RN, MS; Michael Joyner, M.D.; Arturo Casadevall, M.D.; Liise-anne Pirofski, M.D.; Jay Epstein, M.D.; Louis M. Katz, M.D.; Leonard Schleifer, M.D.; George Yancopoulos, M.D.; Eric J. Rubin, M.D.; Philip Drazen, M.D.; Howard Bauchner, M.D.; Catherine D. DeAngelis,

M.D.; Jeffrey P. Henderson, M.D.; Bruce Hall, M.D.; Steven L Liebman, M.D., Richard Stone, M.D. as a legal counsel representative: Jeffrey Rosen, J.D. (former acting Attorney General from December 23, 2020 to January 20, 2021.); representatives from the Association of American Blood Banks (AABB) and the American Red Cross, Dawn O'Connell, J.D., Assistant Secretary for Preparedness and Response, DHHS; etc.

- 4. What could be on the agenda for such a meeting:
 - a. A short course in Clinical Immunology regarding the differences between Active and Passive Immunization presented to the President of the United States and how these agents should be utilized synergistically to end the COVID-19 epidemic in the U.S.A.
 - b. Discussion of how to educate the America public and organize infusion centers around the nation for the EARLY administration of Passive Immunization (Convalescent Plasma, Convalescent Sera, Monoclonal Antibodies, and Monoclonal Antibody Cocktails) and Antiviral agents like Remdesivir. Discussion on how to provide the early administration of Passive Immunization throughout the country. Discuss how to mobilized the nation's blood bank to collect and distribute large quantities of COVID-19 convalescent plasma Fresh Frozen plasma (FFP) as was done during WWII administered initially administrated by Charles Drew, M.D., FACS and the by Eleanor Roosevelt. (Today, in one week, literally with 20 donations daily of COVID-19 Convalescent Plasma (CCP) to the >5000 blood banks throughout the U.S.A., 700,000 units of convalescent FFP can be generated. As there are two doses of 200 ml of "high dose" CCP per FFP unit, 1.4 million units per week are possible. If the FFP is "low dose", doubling the volume to a full unit of FFP (400 ml) will double the polyclonal antibodies administered to an individual (e.g.: 2 or 3 x low dose = one high dose unit of CCP) Most of all, on August 23, 2020 using data from approximately 94,000 units administered late in the disease (the wrong time) by the Mayo Clinic/FDA Expanded Access program (compassionate use of which the data should not have been used) the FDA still concluded that "high dose" was better that "low dose" CCP. Mr. President, would it not seem reasonable that "high dose" is better than NO DOSE!
 - c. Mr. President, with the mortality calculations regarding children under the age of 12 derivable from 1c above, **should a school holiday be declared until such time as all the children can be vaccinated?** Right now we are essentially putting our unvaccinated children who have not contracted previously COVID-19—thus, being individually immunity naïve to COVID-19--in harms way.

Using the equation: y = 0.0008x - 0.0103 R²=0.8254

One can calculate the estimated mortality by year per 100,000/infected.

(But by the least square fit equation derived from the CDC data of 0-45 years, the predicted age range mortalities really predicts finite mortality from age 13 years and above)

Age	Mortality %	Deaths by Age Group
	Infected	100,000 in that Age Group
4 yrs	-0.71%	0
5 yrs	-0.63%	0
6 yrs	-0.55%	0
7 yrs	-0.47%	0
8 yrs	-0.39%	0
9 yrs	-0.31%	0
10 yrs	-0.23%	0
11 yrs	-0.15%	0
12 yrs	-0.07%	0
13 yrs	0.01%	10
14 yrs	0.09%	90
15 yrs	0.17%	170
16 yrs	0.25%	250
17 yrs	0.33%	330
18 yrs	0.41%	410
19 yrs	0.49%	490

d. Discussion of the endpoints regarding full approval of all the agents under EUAs that have demonstrated efficacy by appropriate studies (NOT CCP GIVEN LATE IN THE DISEASE AND LACKING AGE STRATIFIED). The FDA can designate as full-fledged drugs and biologics in the treatment of COVID-19 all the present Passive and Active Immunization agents being utilized by shear numbers of administrations of these agents over the last 18 months when they were give early (<72 hours after diagnosis) and when analyzed by age-stratification!

Mr. President, by now you are probably wondering how we got into this mess. Well, frankly, it was a lot of little errors or presentations of selective transparency that cascaded in misleading and misdirecting U.S. Medicine and the US government.

1. The worst error was constructing administration criteria for CCP and Remdesivir at "deaths-door" rather than within 72 hours of diagnosis. On March 24, 2020, the following FDA announcement based on a misinterpretation of a February 2020 Chinese epidemiology paper published in JAMA which never speaks of treatment of COVID-19 was issued that set into motion administration of CCP at the WRONG TIME, initiated a multitude of NIH clinical trials based on the WRONG TIME, and initiate Clinical Practices of administration of CCP at the WRONG TIME that even now have not been rescinded!:

Investigational COVID-19 Convalescent Plasma - Emergency INDs

March 24, 2020

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https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from public health threats including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to doing everything we can to provide timely response efforts to this pandemic and facilitate access to investigational drugs for use in patients with serious or immediately life-threatening COVID-19 infections.

One investigational treatment being explored for COVID-19 involves the use of convalescent plasma collected from recovered COVID-19 patients. It is possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. Although promising, convalescent plasma has not been shown to be effective in every disease studied. It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so. Investigators wishing to study the use of convalescent plasma are encouraged to submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).

Although participation in clinical trials is one way for patients to obtain access to convalescent plasma, these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the expanding COVID-19 outbreak presents, while clinical trials are being conducted, FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency Investigational New Drug Applications (eINDs) for Individual patients under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This does not include the use of COVID-19 convalescent plasma for the prevention of infection.

Healthcare providers interested in the emergency use of investigational COVID-19 convalescent plasma under a single patient emergency IND should consider the following:

COVID 19 Convalescent Plasma

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Additional considerations for donor eligibility should be addressed, as follows:

- · Prior diagnosis of COVID-19 documented by a laboratory test
- · Complete resolution of symptoms at least 14 days prior to donation
- · Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at <a href="https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices/emergency-use-authorizations-
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug-Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

- . Eligible patients for use under expanded access provisions:
 - Must have laboratory confirmed COVID-19
 - Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or
 - multiple organ dysfunction or failure
 - Must provide informed consent

How to obtain authorization for use of COVID-19 convalescent plasma

- For request that are not highly time sensitive (response from FDA provided within 4 to 8 hours), the requesting
 physician may contact FDA by completing form 3926 (https://www.fda.gov/media/98616/download) and submitting the
 form by email to Covid-19@FDA.HHS.gov.
 - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements of 21 CFR 312.305 and 312.310.
 - o The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
 - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.
 - FDA will review the request and, upon approval, FDA will send the requesting physician a confirmatory email that includes the emergency IND number.
- In the event of an emergency that is highly time sensitive (response required in less than 4 hours) or where the
 provider is unable to complete and submit form 3926 due to extenuating circumstances, the provider may contact
 FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
 - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 15 working days of FDA's authorization of the use.

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

⁵ 1Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72†314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Content current as of: 03/24/2020

A British Medical Journal article: https://www.bmj.com/content/bmj/368/bmj.m1256.full.pdf of March 26, 2020 documented for the world this announcement with it attached three references:

- FDA. Investigational covid-19 convalescent plasma—emergency INDs.

 https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber-investigational-covid-19-convalescent-plasma-emergency-inds (When one attempts to use the Wayback machine to find this site, the response is Wayback Machine has not archived that URL.)
- Hixenbaugh M. FDA will allow doctors to treat critically ill coronavirus patients with flood from survivors. NBC News 2020 Mar 24.

 www.nbcnews.com/news/us-news.com/news/us-news/fda-will-allow-doctors-treat-critically-ill-coronavirus-patients-blood-n1167831 which contains the hyperlink: emergency protocols approved by the FDA which directs to: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma (the February 11, 2021 which is the Wayback Machine first "captured". ****Need to research this more as previous with the Wayback Machine pointed to April 8, 2020)
- Palca J. FDA expedites treatment of seriously ill covid-19 patients with experimental plasma. National Public Radio, 24 Mar 2020.

 www.npr.org/sections/coronavirus-live-updates/2020/03/24/820939536/fda-expedite-treatment-of-seriously-ill-covid-19-patients-with-experimental-plasma which contains the hyperlink: emergency protocols approved by the FDA which directs to: www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma (the February 11, 2021 which is the Wayback Machine first "captured". ****Need to research this more as previous with the Wayback Machine pointed to April 8, 2020)

Reference 1 points to a URL that no longer exists and the other two in the body of the article points to the URL: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drugapplications-inds-cber-regulated-products/recommendations-investigational-covid-19convalescent-plasma of February 11, 2021. Previously, if one copied to this URL into the Wayback Machine of the Internet Archive, the initial document in April 2020 which was an expost facto document of April 8, 2020. This represents Now missing "reference" regarding justification for the criteria incorrectly attributed to the JAMA article of Wu Z, McGoonan JM...(see above)" of the FDA March 24, 2020 announcement. The Incorrect "Eligibility Criteria" criteria was the limiting factor regarding administration of CCP and Remdesivir until September 2, 2020 and August 28, 2020, respectively. The FDA was so "quiet" about these corrections that the VHA issued in November 2020 administration inclusion regarding Remdesivir which was (under the drug name VELKURY) as October 22, 2020 the only FDA fully-approved antiviral (NDA #214787) in the (early) treatment of COVID-19. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf THE WRONG ADMINISTRATION INCLUSION CRITERIA remains the official criteria of the VHA listed on the internet to this day.

https://vanf.app/CFU PDF/Remdesivir VEKLURY November2020.pdf

2. Mr. President, I would suggest you issue an Executive Order banning the present practice across the Executive Branch of the U.S. Government of "Overwriting" official documents. You could then mandate in the Executive Order the reinstatement of the practice that all official documents, policies, directives, and memos of all Departments of the Executive Branch of the U.S. Government document on the face sheet the previous document, policy, directive, and/or memo the present version is replacing the previous replacement document should be recorded in the new version so the new version can be compared by the rescinded version—that is true transparency. At present, if the replacement document is overwritten electronically and the URL is maintained, the replaced/rescinded document can be located, if the URL has not been changed, by utilizing the "Wayback Machine" of the Internet Archive (San Francisco, CA).

---Stopped at this Point----2021-10-20

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20.0 7.0 2021-09-19 Timeline of U.S. Government Regarding Passive Immunization.pdf

150 Emerald Green Ct St. Louis, MO. 63141 August 24, 2022 (edited 8/30/2022) (314) 455-9482

President Joseph Biden
President of the United States of America
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500
202-456-1414

Re: NIH NIAID Case #12276

Dear Mr. President:

Please excuse these volumes of documentation that I have sent to you and the outspoken, unsolicited, forwardness of my appeal to you personally, but our national therapeutic response to COVID-19 has been tantamount to the U.S.P.H.S.'s Tuskegee Syphilis project of four decades in the mid-twentieth century. Yesterday, August 23rd 2022, was the second anniversary of the theoretically-increased-availability of COVID-19 convalescent plasma (polyclonal antibodies) for the entire American public. President Trump used the Press Conference on the evening of August 23rd 2020, before the start of the Republican National Convention to demonstrate himself "presidential" in his concern for all Americans regarding the use of the tried and true treatment methodology of Passive Immunization (convalescent plasma and serum) of the last 135 years. Passive Immunization has been utilized in the initial treatment for many disease-entities for which Karl von Bering was awarded the first Noble Prize in Medicine and Physiology and Medicine and has one of its origins in Louis Pasteur's rabies-treatment of Joseph Meiter, a nine year-old boy with extensive dog bites from a rabid dog in 1885. Convalescent plasma and sera have been used successfully in in the multitude of maladies and prevention of subsequent medical conditions: rabies; hydrops fetalis (Rhogam); tetanus-prone wounds (Hypertet); treatment of novel viruses when vaccines did not exist; treatment of bacteria when antibiotics were unknown and unavailable; in small pox in newly, unvaccinated, diagnosed cases and contacts; insect and snake envenomations; etc. Between April 4, 2020 and August 23, 2020, through the FDA/Mayo Clinic expanded access (compassionate use) protocol greater than 94,000 units of convalescent plasma were administered late, at the **wrong late administration time** (>72 hours). The wrong-time administration protocol was quietly removed from all subsequent EUAs by the FDA Chief Scientist, Denise Hinton, R.N., M.S., who at present is the Deputy Surgeon General of the United States—but for months later, the practice was wrongly continued as the VHA initiated in November 2020 (Attachment A). With regards to President Trump's gambit, it backfired.—Researchers and physicians of Academic/University Medicine pounced and declared COVID-19 Convalescent Plasma was probably not very useful. Instead of making COVID-19 Convalescent Plasma more available to be given within the first 72 hours of diagnosis or symptomatology, it has been and was **WRONGLY** administered late (>72 hours) in the disease during the phases of cytokine cascade and bradykinin storm in which no antibody would be very effective in the aggregate when used at death's door. This medical stupidity was

promoted by academic medicine and federal medicine (FDA, NIH, CDC, PHS, BARDA...) resulting in over a million preventable deaths. In short, this was analogous to a Tuskegee syphilis project "mindset" which was wrongly promoted, wrongly implemented, and wrongly applied across the nation.

Attached to this cover letter are 15 letters that I wrote to you since the start of your administration that I never sent as they each addressed separate distinct errors in medical statistics, medical definitions and terminology, administration of appropriate therapeutics, and outright abandonment by the FDA, NIH, University Research Medicine, etc.—in short, it was like *The blind men and the elephant*. Also attached on the data card is a chronologic reference bibliography of over 1187 references regarding COVID-19 justifying every statement I have made in this cover letter:

<u>2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where</u> we went wrong > 05 Timeline Bibliography > **10** 2022-05-30 Bibliographic Timeline <u>References</u>

--- and also on the attached data card is a more complete parallel annotated bibliography with quotes, analysis, and relevance linkage:

<u>2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where</u> we went wrong > 05 Timeline Bibliography > **20** 2022-05-30 annotated Bibliographic <u>Timeline References</u>.

Instigated by announcements publicly of four unrecognized medical errors publicly in March 2020, America has therapeutically gone ignorantly down-the-rabbit-hole:

- 1. March 2, 2020: In a *White House* conference https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus of President Trump, Vice-President Pence, physicians of the Executive Branch of the U.S. Federal Government, and Physicians and CEO's of the Pharmaceutical Industry, Dr. Leonard Scheifler, M.D., PhD, CEO of Regeneron Pharmaceuticals, https://www.youtube.com/watch?v=31i6p_stzW8 incorrectly answered President Trump's inquiry about the difference of vaccines vs monoclonal antibodies by explaining *Passive Vaccination* (which is a misnomer) and does NOT exit:
 - a. Active Immunization: Vaccination with Antigens IM which require 14 days for the development of IgG against COVID-19. (Mr. President, the reason your wife and you, have recently tested positive is that you, like all "vaccinated Americans" were not vaccinated with a nasal spray so as to develop IgA.—so, while your symptoms were muted by two primary IM vaccinations and two boosters that stimulated endogenous IgM and IgG, you never produced IgA in you nares until your recent infection.)
 - b. **Passive Immunization:** Immunoglobulins administered **EARLY** (<72 hours):

- i. COVID-19 Convalescent Plasma (CCP) which is cheap, safe, and readily available through the collection, testing, and processing by the Blood Banks of America (Early administration of CCP was ignored at that March 2, 2020 meeting as neither representatives of the AABB (Association of American Blood Banks) nor the America Red Cross were invited to the table.)
- ii. Monoclonal Antibodies and Antibody cocktails which are expensive, safe, and but are subject to COVID-19 developing resistance as they are only one or two antibodies and **NOT** polyclonal antibodies like COVID-19 Convalescent Plasma.
- 2. March 13, 2022: U.S. DHHS Secretary Alex Azar announced http://www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx the suspension of parts of EMTALA retroactive to March 1, 2020 thus negating / abridging *de facto* the rights of all Americans to ask for Early Administration (<72 hours from diagnosis / symptomatology) of COVID-19 Convalescent Plasma (or immunoglobulins) and the initially available antiviral, Remdesivir, which since October 22, 2020, has been a prescription drug, FDA NDA #214787, in the treatment of COVID-19 that can be prescribed by any M.D. or D.O. legally in all 50 states, D.C., and other sites of the U.S.A. that could be infused for 3 5 days, twice a day, early (<72 96 hours) in the course of the individual patient's COVID-19 in Every Man, Woman, and Child that had and will contract SARS-CoV-2 (COVID-19).</p>
- 3. March 18, 2020: U.S. PHS Surgeon General Adams advised in a PSA to all Americans NOT to go to the hospital if they were possibly sick with COVID-19 which *de facto* abandoned Every Man, Woman, and Child that had and will contract SARS-CoV-2 (COVID-19). https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/
- 4. March 24, 2020: The FDA announced **INCORRECT** inclusion criteria for the administration of COVID-19 Convalescent Plasma based on an **INCORRECT** interpretation of an epidemiology article from Wuhan China published in the Journal of the American Medical Association:

After reading this cover letter, the 15 accompanying letters, and other pertinent documentation, Mr. President, you can confirm that which I'm saying to you by calling on Anthony Fauci, M.D. and Francis Collins, M.D. Ask of them, as you are our boss of the Executive Branch of the Federal Government, to write a monograph for you explaining the pathophysiology of COVID-19 convalescent plasma and the initiation of appropriate **early administration of immunoglobulins and antivirals** in the treatment of a novel virus like SARS-CoV-2 (COVID-19) universally for all! If you wish, I, as a VHA physician and surgeon, will construct for you, Mr. President, a much-needed clinically-focused "chapter" for the **individual patient** for a medical textbook on the pathophysiology of SARS-Cov-2, testing, prevention methods and vaccination, early therapeutics in those COVID-19 infected (<72 hours) with immunoglobulins

and antivirals, and supportive treatment late in the disease (>72-96 hours). [Attachment B is a diagrammatic representation of COVID-19 pathophysiology.]

Mr. President, how has the extensive COVID-19 tragedy of the morbidities and mortalities in America been augmented and facilitated? -- we have de facto substituted for our motto: In God We Trust with that of which we faulted the Communists during the Cold War: The end justifies the means. Did you know that the word *Propaganda* comes from the root phase "to propagate" as epitomized by the name of the missionary society of the Catholic Church: The Society for the Propagation of the Faith? A half a century ago, President Gerald Ford probably lost his election bid to continue as President of the United States because he put the country's well-being above his own political solvency by pardoning President Richard Nixon. Unfortunately, while all criminal prosecution was immediately curtailed and the pardon helped America heal, lawyers around the country had the mindset that they could still sue the President of the United States in civil litigation. In 1982, the Brennan Supreme Court ruled in a 5-4 decision in favor of President Nixon in Nixon v Fitzgerald. This decision is the reason why all subsequent Presidents have had absolute immunity from all civil litigation. Before and throughout President Trump's four years in office, he abused this ruling by lying to the American public over 30,000 times. In the opinion of the Court, there were two safeguards that would prevent or diminish such abuse: (1) the Constitutional imperative of Impeachment of the President of the United States for "high crimes and misdemeanors" and the *de facto* oversight by the Press. As the amoral businessman President Trump has been throughout his life, he persists, even to this day, with ad hominem attacks on any person that opposes his agenda which is his (as is every American's) right under the First Amendment. The intent of First Amendment was not to promote nor guarantee irresponsible behavior, though, as "crying FIRE" in a theater, etc. What is more, while the January 6th Commission of the U.S. House of Representatives is correctly chipping away at President Trump's façade, by his Senatorial acquittal in his second Impeachment Trial, President Trump is protected from any future prosecution regarding his involvement in the January 6th, 2021 insurrection by the Constitutional prohibition of double jeopardy afforded to all by the Fifth Amendment.

If, as I state, the compendium of attached documentation regarding American Medicine's response to COVID-19 was a BIG medical mistake, what's in it for Federal and Academic Medicine and Research? In 2018, President Trump signed into law PL-115-176: TRICKETT WENDLER, FRANK MONGIELLO, JORDAN MCLINN, AND MATTHEW BELLINA RIGHT TO TRY ACT OF 2017. Per PL-115-176, the right of every American to ask for any experimental (under an EUA) drug or biologic is absolute and is guaranteed provided a Phase I Trial (a Safety Study) has been *completed*. – For the Medical Researcher, Clinical Grant Awardee, and the Universities, Pharmaceutical Companies, the Medical Device Manufacturers, the status quo of medical research in the United States must irreparably change by PL-115-176. So, what has the FDA and NIH done?--they have failed to declare any therapies in the treatment COVID-19 officially "safe" and have merged the concepts of "safety—Phase I clinical trials" with "efficacy—Phase II-III clinical trials" thus de facto proscribing the application and circumventing the intent of PL-155-176--even when there is appropriate scientific proof of the safety of COVID-19 Convalescent Plasma (polyclonal antibodies) reported in over 94,000 administrations late in the pathology of the disease in individual Americans. Mr. President, why don't you ask Drs. Fauci and Collins: Why has early

administration (within 72-96 hours of symptomatology or diagnosis) of COVID-19 Convalescent Plasma, other Immoglobulin agents, and antiviral agents not been nationally advocated nor universally announced for all Americans? COVID-19 Convalescent Plasma (CCP) has been available since the start of the American epidemic in March 2020. It could easily be collected and processed by the blood banks of America (both private, propriety blood banks, and those administered by the American Red Cross). Every hospital and outpatient infusion center in the nation could and should have administered a one-time dose (or more if it is "low dose") through outpatient and inpatient infusion centers across the nation. Like that during WWII when first director of the American blood drive, Charles Drew, M.D., F.A.C.S., and later Eleanor Roosevelt as Directors of the American Red Cross promoted plasma collection (especially for the war in the South Pacific where whole blood in acid-citrate, the only available anticoagulant at the time, had a shelf-life in a refrigerator of two weeks which precluded an Ocean voyage). All units of fresh frozen plasma today (like COVID-19 Convalescent Plasma) are collected in CPD or CP2D having shelf-lives of ~ 1 year, and CCP is readily available by donation, effective in "high titer", and cheap to collect, process, and distribute.

So Mr. President, why was PL-115-176 so threatening to the Medical-University-Pharmaceutical Industrial Complex? Well,...

1. Recruitment for Randomized Control Trials (RCT) would be impossible with the inability to investigate patients potentially for **placebo** groups. On August 12, 2020, when one of the named investigators of the FDA/Mayo Expanded Access (Compassionate Use) was asked this very question, the researcher's response was the following which is inconsistent with the Nuremburg Code, the Helsinki Accords, and the Belmont Report and should be denounced as coercion by every Intuitional Review Board (IRBs are all overseen by the FDA) in the United States of America:

Since April, the Trump administration has set aside **more than \$300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving high-risk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

2. Having been a VA Merit II Grant research recipient in the early 1990s in which the nominal award is the absolute total money received, the NIH Grants have funded medical researchers and the Universities are very cognizant that in the past the indirect moneys may almost double the awards. Is it so hard to reason why few researchers have questioned the NIH direction in the treatment of COVID-19? Application of PL-115-176 stifles all present and future RCTs by permitted every American the right of request for a Phase I-completed without having to participate in a RCTs.—BUT, PL-115-176 IS THE LAW OF THE LAND!

- 3. In November 2020, the local VA Infectious Diseases service of the St. Louis VAMC ordered the discontinuation of Remdesivir prescribed for my patients citing the VACO protocol in Attachment A. (This VA protocol has been completely wiped from the Internet subsequently probably by the VA.) The correspondence interaction between myself, the VA, Dr. Fauci's office, and the editors of *The New England Journal of Medicine* can be found in the attached data card in: 2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where we went wrong > 06 Appendices A-H > Appendix E—Correspondence with VA and NEJM Dec 2020.
- 4. On February 18, 2021, *The New England Journal of Medicine* published a three page editorial as an excuse for what subliminally had occurred for the previous 11 months regarding *Passive Immunization* in the FDA/NIH disorganized treatment of COVID-19. Louis Katz, M.D., former Chief Medical Officer at America's Blood Bank Center in Washington, was the sole author of this editoral: Katz LM: (A Little) Clarity on convalescent plasma for Covid-19. Initially published electronically on January 13, 2021, and republished as a hardcopy republished in the N Engl J Med, 2021 Feb 18; 384 (7): 666 668. https://www.nejm.org/doi/full/10.1056/NEJMe2035678. On March 2, 2021:
 - 783) NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health announcement is: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms

The actual clinic trial, *Convalescent Plasma in Outpatients with COVID-19 (SIREN C3PO)* NCT04355767, was: https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&d raw=2&rank=1

There were no reported results on the NIH ClinicalTrials website of which the NIH was making its decision to halt the trial. The trial was underpowered where there was no stratification by age, the exclusion criteria were arbitrary to an extreme, and the study was discontinued with recruitment of only half the number of planned patients. This study was run by: SIREN, Strategies to Innovate emeRgENcy Care Clinical Trials, https://clic-ctsa.org/node/9426.

The actual "results of this RCT" were finally published in hard-copy form on November 18, 2022. In my opinion, *this article is one of the most disingenuous research papers I have ever read*—and was unbecoming of *The New England Journal of Medicine*:

1014) 2021-11-18 Korley FK, Durkalski-Mauldin V, Yeatts SD, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswall S, Kaplan A, Lowell E, Mcdyer JF, Quinn J, Triulzi DJ, Van Huysen C, Stevenson VLM, Yadav K, Jones CW, Kea B, Burnett A, Reynolds JC, Greineder CF, Haas NL, Beiser DG, Silbergleit

R, Barsa W, Callaway CW, for the SIREN-C3PO Investigators: Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO ClinicalTrials.gov number, NCT04355767.] https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true

The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. (Advarra is a propriety company which on their internet listing are: Industry Experts—The Advarra Advantage: Our Expertise:

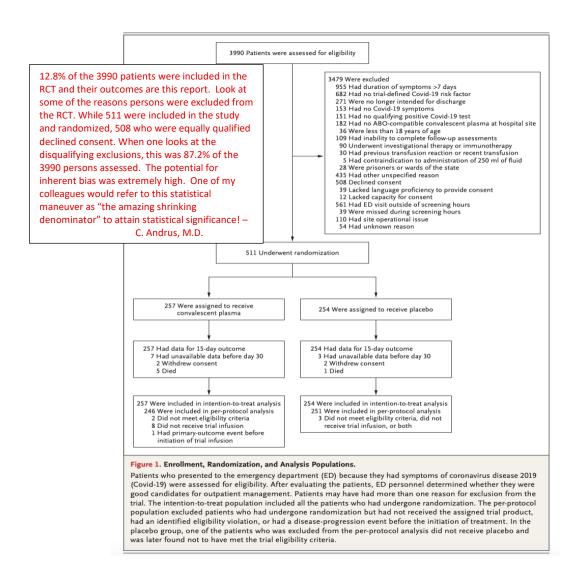
The Advarra advantage is built on our industry and domain expertise. Our experts are change agents and thought leaders with deep experience in clinical research. Together, we solve mission-critical challenges and bring life-changing therapies to participants faster. (Please note, Advarra's experts listed on their website https://www.advarra.com/about/industry-experts/ include **NO MEDICAL**CLINICIANS LIKE AN M.D. OR A D.O. In short, the SIREN-C3PO clinical trial NCT04355767 was reviewed by a proprietary company and **NOT** by any University School of Medicine IRB, any participating Hospital IRB, or the FDA's IRB directly.)

PLEASE note that the complete article and the supplementary appendix can be found:

Korley FK, Durkalski-Maudin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, et al., for the DIREN-C3PO Investigators*: Early convalescent plasma for high-risk outpatients with Covid-19. URL from article N Engl J Med 2021 Nov 18; 385: 1951-1960.

https://www.nejm.org/doi/10.1056/NEJMoa2103784 This reference from the article is just an abbreviation; The full article is

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true and the Supplementary Appendix which is very important can be found at (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf).



In Figure 1. **Enrollment, Randomization, and Analysis Populations**, of the 3990 patients presenting to the Emergency Room, 3479 (87.2%) were excluded as listed in the box above. The number of eligible patients that refused to participate in this placebo RCT was 508 and with the 561 that presented outside of ED screening hours and thus were rejected. These two exclusion factors totaled over twice as many patients (1069) as were included in this study of 511. What is more, when the NIH announced the closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum \(\beta \) that the researchers agreed upon for a valid study), it proceeded to conclude that early administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is most probably a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published.

It should also be noted that at the end of the author list on the front page of this article, it is stated: ...for the SIREN-C3PO Investigators* where the "**" refers to the statement in the right margin:

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org which is 20 pages long (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf) In this Supplementary Appendix major criteria for inclusion in the study changed from Protocol Version 1 of June 17, 2020 through Version 2 of July 2, 2020, Version 3 of September 7, 2020, Version 4 of November 3, 2020 to Version 5, February 16, 2021:

Has at least one study defined risk factor for severe COVID-19 illness:

Age \geq 50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression

Yet, in Table 1. Characteristics of the Patients at Baseline:

Characteristic	Convalescent Plasma	Placebo	
	(N=257)	(N=254)	
Median age (IQR)	54 (42-62)	54 (40-62)	

there were patients of 42-49 years in the Convalescent Plasma group and patients of 40-49 years in the placebo group. Those patients should have been excluded due to their "youngness" that violated the stated inclusion criteria of all five Protocol versions of this trial. Were the SIREN-C3PO investigators, the NIH, and the editors of *The New England Journal of Medicine* being truthful to the American public? Has this paper done a disservice to the American public and to the World? As the NEJM attests to the participation in the *International Committee of Medical Journal Editors (ICMJE)*, they owe the American people an independent (independent from the U.S. Government and *The New England Journal of Medicine*) peer review of this paper with regards to appropriateness: Simply put, can this paper even conclude that which it concludes?

Mr. President, I apologize for the length of this cover letter trying to provide an overview summary of what is contained in my submission to you today. Besides suggesting that you have Drs. Fauci and Collins write monographs for you regarding the Pathophysiology of COVID-19 and therapies based on treating the pathophysiology, there are foundational flaws in our medical system that require addressing: failure of the IRBs; failure to implement PL-115-176, The Right to Try law; abridgement of American rights guaranteed by EMTALA; etc. to name but a few.

If I can provide clarification or suggestions in the future, please ask whatever you may of me as I am a physician and surgeon of the Veterans Health Administration, U.S. Department of Veterans Affairs. (This weekend our family drove to Atlanta as our second son (we have five boys) got married—now that our family is home, should you wish one of your people to contact me,

please call my wife Pam's cell phone: 314-809-9634 or our home phone: 314-455-9482. Thank you for taking this information under your consideration.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.

Former Professor of Surgery, Department of Surgery, Saint Louis University School of Medicine Physician and Surgeon and Chief of Unit II (SLU) General Surgery division, Surgical Service, St. Louis (John Cochran) VAMC

Home phone: 314-455-9482

Pam's cell: 314-809-9634

Cc:

Anthony S. Fauci, M.D.
Director of the U.S. NIAID
U.S. National Institutes of Health
U.S. Dept of Health & Human Services
5601 Fishers Lane, MSC. 9806
Bethesda, MD. 20892-9806
Re: Case # 12276

Phone: 301-496-5717 FAX: 301-402-3573

The Honorable Denis McDonough Secretary, U.S. Department of Veterans Affairs 810 Vermont Ave, NW Washington, DC. 20420 Denis.McDonough@va.gov

Catherine Mitrano, J.D. and Michael R. Hogan, J.D. Office of General Counsel (26)
Designated Agency Ethics Official (DAEO)
810 Vermont Ave, NW
Washington, D.C. 20420

Phone: 202-360-3598

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20.0 7.0 2021-09-19 Timeline of U.S. Government Regarding Passive Immunization.pdf

150 Emerald Green Ct St. Louis, MO. 63141 August 24, 2022 (edited 8/30/2022) (314) 455-9482

President Joseph Biden
President of the United States of America
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500
202-456-1414

Re: NIH NIAID Case #12276

Dear Mr. President:

Please excuse these volumes of documentation that I have sent to you and the outspoken, unsolicited, forwardness of my appeal to you personally, but our national therapeutic response to COVID-19 has been tantamount to the U.S.P.H.S.'s Tuskegee Syphilis project of four decades in the mid-twentieth century. Yesterday, August 23rd 2022, was the second anniversary of the theoretically-increased-availability of COVID-19 convalescent plasma (polyclonal antibodies) for the entire American public. President Trump used the Press Conference on the evening of August 23rd 2020, before the start of the Republican National Convention to demonstrate himself "presidential" in his concern for all Americans regarding the use of the tried and true treatment methodology of Passive Immunization (convalescent plasma and serum) of the last 135 years. Passive Immunization has been utilized in the initial treatment for many disease-entities for which Karl von Bering was awarded the first Noble Prize in Medicine and Physiology and Medicine and has one of its origins in Louis Pasteur's rabies-treatment of Joseph Meiter, a nine year-old boy with extensive dog bites from a rabid dog in 1885. Convalescent plasma and sera have been used successfully in in the multitude of maladies and prevention of subsequent medical conditions: rabies; hydrops fetalis (Rhogam); tetanus-prone wounds (Hypertet); treatment of novel viruses when vaccines did not exist; treatment of bacteria when antibiotics were unknown and unavailable; in small pox in newly, unvaccinated, diagnosed cases and contacts; insect and snake envenomations; etc. Between April 4, 2020 and August 23, 2020, through the FDA/Mayo Clinic expanded access (compassionate use) protocol greater than 94,000 units of convalescent plasma were administered late, at the **wrong late administration time** (>72 hours). The wrong-time administration protocol was quietly removed from all subsequent EUAs by the FDA Chief Scientist, Denise Hinton, R.N., M.S., who at present is the Deputy Surgeon General of the United States—but for months later, the practice was wrongly continued as the VHA initiated in November 2020 (Attachment A). With regards to President Trump's gambit, it backfired.—Researchers and physicians of Academic/University Medicine pounced and declared COVID-19 Convalescent Plasma was probably not very useful. Instead of making COVID-19 Convalescent Plasma more available to be given within the first 72 hours of diagnosis or symptomatology, it has been and was **WRONGLY** administered late (>72 hours) in the disease during the phases of cytokine cascade and bradykinin storm in which no antibody would be very effective in the aggregate when used at death's door. This medical stupidity was

promoted by academic medicine and federal medicine (FDA, NIH, CDC, PHS, BARDA...) resulting in over a million preventable deaths. In short, this was analogous to a Tuskegee syphilis project "mindset" which was wrongly promoted, wrongly implemented, and wrongly applied across the nation.

Attached to this cover letter are 15 letters that I wrote to you since the start of your administration that I never sent as they each addressed separate distinct errors in medical statistics, medical definitions and terminology, administration of appropriate therapeutics, and outright abandonment by the FDA, NIH, University Research Medicine, etc.—in short, it was like *The blind men and the elephant*. Also attached on the data card is a chronologic reference bibliography of over 1187 references regarding COVID-19 justifying every statement I have made in this cover letter:

<u>2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where</u> we went wrong > 05 Timeline Bibliography > **10** 2022-05-30 Bibliographic Timeline <u>References</u>

--- and also on the attached data card is a more complete parallel annotated bibliography with quotes, analysis, and relevance linkage:

<u>2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where</u> we went wrong > 05 Timeline Bibliography > **20** 2022-05-30 annotated Bibliographic <u>Timeline References</u>.

Instigated by announcements publicly of four unrecognized medical errors publicly in March 2020, America has therapeutically gone ignorantly down-the-rabbit-hole:

- 1. March 2, 2020: In a *White House* conference https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus of President Trump, Vice-President Pence, physicians of the Executive Branch of the U.S. Federal Government, and Physicians and CEO's of the Pharmaceutical Industry, Dr. Leonard Scheifler, M.D., PhD, CEO of Regeneron Pharmaceuticals, https://www.youtube.com/watch?v=31i6p_stzW8 incorrectly answered President Trump's inquiry about the difference of vaccines vs monoclonal antibodies by explaining *Passive Vaccination* (which is a misnomer) and does NOT exit:
 - a. Active Immunization: Vaccination with Antigens IM which require 14 days for the development of IgG against COVID-19. (Mr. President, the reason your wife and you, have recently tested positive is that you, like all "vaccinated Americans" were not vaccinated with a nasal spray so as to develop IgA.—so, while your symptoms were muted by two primary IM vaccinations and two boosters that stimulated endogenous IgM and IgG, you never produced IgA in you nares until your recent infection.)
 - b. **Passive Immunization:** Immunoglobulins administered **EARLY** (<72 hours):

- i. COVID-19 Convalescent Plasma (CCP) which is cheap, safe, and readily available through the collection, testing, and processing by the Blood Banks of America (Early administration of CCP was ignored at that March 2, 2020 meeting as neither representatives of the AABB (Association of American Blood Banks) nor the America Red Cross were invited to the table.)
- Monoclonal Antibodies and Antibody cocktails which are expensive, safe, and but are subject to COVID-19 developing resistance as they are only one or two antibodies and NOT polyclonal antibodies like COVID-19 Convalescent Plasma.
- 2. March 13, 2022: U.S. DHHS Secretary Alex Azar announced http://www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx the suspension of parts of EMTALA retroactive to March 1, 2020 thus negating / abridging *de facto* the rights of all Americans to ask for Early Administration (<72 hours from diagnosis / symptomatology) of COVID-19 Convalescent Plasma (or immunoglobulins) and the initially available antiviral, Remdesivir, which since October 22, 2020, has been a prescription drug, FDA NDA #214787, in the treatment of COVID-19 that can be prescribed by any M.D. or D.O. legally in all 50 states, D.C., and other sites of the U.S.A. that could be infused for 3 5 days, twice a day, early (<72 96 hours) in the course of the individual patient's COVID-19 in Every Man, Woman, and Child that had and will contract SARS-CoV-2 (COVID-19).</p>
- 3. March 18, 2020: U.S. PHS Surgeon General Adams advised in a PSA to all Americans NOT to go to the hospital if they were possibly sick with COVID-19 which *de facto* abandoned Every Man, Woman, and Child that had and will contract SARS-CoV-2 (COVID-19). https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/
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and antivirals, and supportive treatment late in the disease (>72-96 hours). [Attachment B is a diagrammatic representation of COVID-19 pathophysiology.]

Mr. President, how has the extensive COVID-19 tragedy of the morbidities and mortalities in America been augmented and facilitated? -- we have de facto substituted for our motto: In God We Trust with that of which we faulted the Communists during the Cold War: The end justifies the means. Did you know that the word *Propaganda* comes from the root phase "to propagate" as epitomized by the name of the missionary society of the Catholic Church: The Society for the Propagation of the Faith? A half a century ago, President Gerald Ford probably lost his election bid to continue as President of the United States because he put the country's well-being above his own political solvency by pardoning President Richard Nixon. Unfortunately, while all criminal prosecution was immediately curtailed and the pardon helped America heal, lawyers around the country had the mindset that they could still sue the President of the United States in civil litigation. In 1982, the Brennan Supreme Court ruled in a 5-4 decision in favor of President Nixon in Nixon v Fitzgerald. This decision is the reason why all subsequent Presidents have had absolute immunity from all civil litigation. Before and throughout President Trump's four years in office, he abused this ruling by lying to the American public over 30,000 times. In the opinion of the Court, there were two safeguards that would prevent or diminish such abuse: (1) the Constitutional imperative of Impeachment of the President of the United States for "high crimes and misdemeanors" and the *de facto* oversight by the Press. As the amoral businessman President Trump has been throughout his life, he persists, even to this day, with ad hominem attacks on any person that opposes his agenda which is his (as is every American's) right under the First Amendment. The intent of First Amendment was not to promote nor guarantee irresponsible behavior, though, as "crying FIRE" in a theater, etc. What is more, while the January 6th Commission of the U.S. House of Representatives is correctly chipping away at President Trump's façade, by his Senatorial acquittal in his second Impeachment Trial, President Trump is protected from any future prosecution regarding his involvement in the January 6th, 2021 insurrection by the Constitutional prohibition of double jeopardy afforded to all by the Fifth Amendment.

If, as I state, the compendium of attached documentation regarding American Medicine's response to COVID-19 was a BIG medical mistake, what's in it for Federal and Academic Medicine and Research? In 2018, President Trump signed into law PL-115-176: TRICKETT WENDLER, FRANK MONGIELLO, JORDAN MCLINN, AND MATTHEW BELLINA RIGHT TO TRY ACT OF 2017. Per PL-115-176, the right of every American to ask for any experimental (under an EUA) drug or biologic is absolute and is guaranteed provided a Phase I Trial (a Safety Study) has been *completed*. – For the Medical Researcher, Clinical Grant Awardee, and the Universities, Pharmaceutical Companies, the Medical Device Manufacturers, the status quo of medical research in the United States must irreparably change by PL-115-176. So, what has the FDA and NIH done?--they have failed to declare any therapies in the treatment COVID-19 officially "safe" and have merged the concepts of "safety—Phase I clinical trials" with "efficacy—Phase II-III clinical trials" thus de facto proscribing the application and circumventing the intent of PL-155-176--even when there is appropriate scientific proof of the safety of COVID-19 Convalescent Plasma (polyclonal antibodies) reported in over 94,000 administrations late in the pathology of the disease in individual Americans. Mr. President, why don't you ask Drs. Fauci and Collins: Why has early

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1. Recruitment for Randomized Control Trials (RCT) would be impossible with the inability to investigate patients potentially for **placebo** groups. On August 12, 2020, when one of the named investigators of the FDA/Mayo Expanded Access (Compassionate Use) was asked this very question, the researcher's response was the following which is inconsistent with the Nuremburg Code, the Helsinki Accords, and the Belmont Report and should be denounced as coercion by every Intuitional Review Board (IRBs are all overseen by the FDA) in the United States of America:

Since April, the Trump administration has set aside **more than \$300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving high-risk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

2. Having been a VA Merit II Grant research recipient in the early 1990s in which the nominal award is the absolute total money received, the NIH Grants have funded medical researchers and the Universities are very cognizant that in the past the indirect moneys may almost double the awards. Is it so hard to reason why few researchers have questioned the NIH direction in the treatment of COVID-19? Application of PL-115-176 stifles all present and future RCTs by permitted every American the right of request for a Phase I-completed without having to participate in a RCTs.—BUT, PL-115-176 IS THE LAW OF THE LAND!

- 3. In November 2020, the local VA Infectious Diseases service of the St. Louis VAMC ordered the discontinuation of Remdesivir prescribed for my patients citing the VACO protocol in Attachment A. (This VA protocol has been completely wiped from the Internet subsequently probably by the VA.) The correspondence interaction between myself, the VA, Dr. Fauci's office, and the editors of *The New England Journal of Medicine* can be found in the attached data card in: 2022-08-24 Submission to NIAID 12276 > 4.0 Dear Mr. President COVID-19 and where we went wrong > 06 Appendices A-H > Appendix E—Correspondence with VA and NEJM Dec 2020.
- 4. On February 18, 2021, *The New England Journal of Medicine* published a three page editorial as an excuse for what subliminally had occurred for the previous 11 months regarding *Passive Immunization* in the FDA/NIH disorganized treatment of COVID-19. Louis Katz, M.D., former Chief Medical Officer at America's Blood Bank Center in Washington, was the sole author of this editoral: Katz LM: (A Little) Clarity on convalescent plasma for Covid-19. Initially published electronically on January 13, 2021, and republished as a hardcopy republished in the N Engl J Med, 2021 Feb 18; 384 (7): 666 668. https://www.nejm.org/doi/full/10.1056/NEJMe2035678. On March 2, 2021:
 - 783) NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health announcement is: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms

The actual clinic trial, *Convalescent Plasma in Outpatients with COVID-19 (SIREN C3PO)* NCT04355767, was: https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&d raw=2&rank=1

There were no reported results on the NIH ClinicalTrials website of which the NIH was making its decision to halt the trial. The trial was underpowered where there was no stratification by age, the exclusion criteria were arbitrary to an extreme, and the study was discontinued with recruitment of only half the number of planned patients. This study was run by: SIREN, Strategies to Innovate emeRgENcy Care Clinical Trials, https://clic-ctsa.org/node/9426.

The actual "results of this RCT" were finally published in hard-copy form on November 18, 2022. In my opinion, *this article is one of the most disingenuous research papers I have ever read*—and was unbecoming of *The New England Journal of Medicine*:

1014) 2021-11-18 Korley FK, Durkalski-Mauldin V, Yeatts SD, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswall S, Kaplan A, Lowell E, Mcdyer JF, Quinn J, Triulzi DJ, Van Huysen C, Stevenson VLM, Yadav K, Jones CW, Kea B, Burnett A, Reynolds JC, Greineder CF, Haas NL, Beiser DG, Silbergleit

R, Barsa W, Callaway CW, for the SIREN-C3PO Investigators: Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med 2021 Nov 18; 385 (21): 1951-1960. [SIREN-C3PO ClinicalTrials.gov number, NCT04355767.] https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true

The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. (Advarra is a propriety company which on their internet listing are: Industry Experts—The Advarra Advantage: Our Expertise:

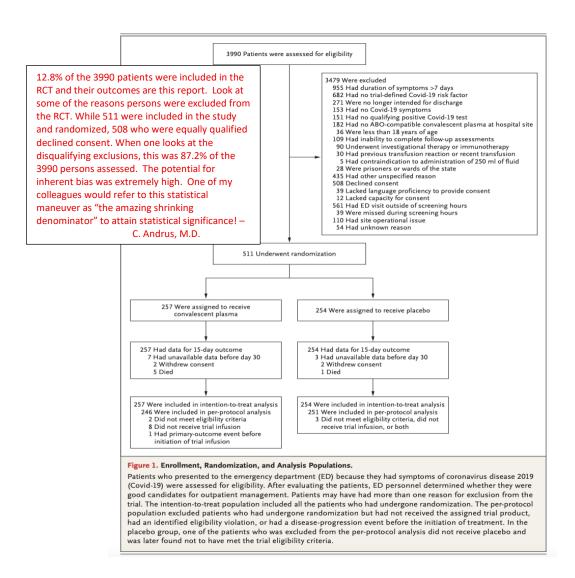
The Advarra advantage is built on our industry and domain expertise. Our experts are change agents and thought leaders with deep experience in clinical research. Together, we solve mission-critical challenges and bring life-changing therapies to participants faster. (Please note, Advarra's experts listed on their website https://www.advarra.com/about/industry-experts/ include NO MEDICAL CLINICIANS LIKE AN M.D. OR A D.O. In short, the SIREN-C3PO clinical trial NCT04355767 was reviewed by a proprietary company and NOT by any University School of Medicine IRB, any participating Hospital IRB, or the FDA's IRB directly.)

PLEASE note that the complete article and the supplementary appendix can be found:

Korley FK, Durkalski-Maudin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, et al., for the DIREN-C3PO Investigators*: Early convalescent plasma for high-risk outpatients with Covid-19. URL from article N Engl J Med 2021 Nov 18; 385: 1951-1960.

https://www.nejm.org/doi/10.1056/NEJMoa2103784 This reference from the article is just an abbreviation; The full article is

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true and the Supplementary Appendix which is very important can be found at (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784 appendix.pdf).



In Figure 1. **Enrollment, Randomization, and Analysis Populations**, of the 3990 patients presenting to the Emergency Room, 3479 (87.2%) were excluded as listed in the box above. The number of eligible patients that refused to participate in this placebo RCT was 508 and with the 561 that presented outside of ED screening hours and thus were rejected. These two exclusion factors totaled over twice as many patients (1069) as were included in this study of 511. What is more, when the NIH announced the closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum \(\beta \) that the researchers agreed upon for a valid study), it proceeded to conclude that early administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is most probably a skewed, underpowered trial which the NIH and the editors of *The New England Journal of Medicine* should never have published.

It should also be noted that at the end of the author list on the front page of this article, it is stated: ...for the SIREN-C3PO Investigators* where the "**" refers to the statement in the right margin:

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org which is 20 pages long (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa2103784_appendix.pdf) In this Supplementary Appendix major criteria for inclusion in the study changed from Protocol Version 1 of June 17, 2020 through Version 2 of July 2, 2020, Version 3 of September 7, 2020, Version 4 of November 3, 2020 to Version 5, February 16, 2021:

Has at least one study defined risk factor for severe COVID-19 illness:

Age \geq 50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression

Yet, in Table 1. Characteristics of the Patients at Baseline:

Characteristic	Convalescent Plasma	Placebo	
	(N=257)	(N=254)	
Median age (IQR)	54 (42-62)	54 (40-62)	

there were patients of 42-49 years in the Convalescent Plasma group and patients of 40-49 years in the placebo group. Those patients should have been excluded due to their "youngness" that violated the stated inclusion criteria of all five Protocol versions of this trial. Were the SIREN-C3PO investigators, the NIH, and the editors of *The New England Journal of Medicine* being truthful to the American public? Has this paper done a disservice to the American public and to the World? As the NEJM attests to the participation in the *International Committee of Medical Journal Editors (ICMJE)*, they owe the American people an independent (independent from the U.S. Government and *The New England Journal of Medicine*) peer review of this paper with regards to appropriateness: Simply put, can this paper even conclude that which it concludes?

Mr. President, I apologize for the length of this cover letter trying to provide an overview summary of what is contained in my submission to you today. Besides suggesting that you have Drs. Fauci and Collins write monographs for you regarding the Pathophysiology of COVID-19 and therapies based on treating the pathophysiology, there are foundational flaws in our medical system that require addressing: failure of the IRBs; failure to implement PL-115-176, The Right to Try law; abridgement of American rights guaranteed by EMTALA; etc. to name but a few.

If I can provide clarification or suggestions in the future, please ask whatever you may of me as I am a physician and surgeon of the Veterans Health Administration, U.S. Department of Veterans Affairs. (This weekend our family drove to Atlanta as our second son (we have five boys) got married—now that our family is home, should you wish one of your people to contact me,

please call my wife Pam's cell phone: 314-809-9634 or our home phone: 314-455-9482. Thank you for taking this information under your consideration.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.

Former Professor of Surgery, Department of Surgery, Saint Louis University School of Medicine Physician and Surgeon and Chief of Unit II (SLU) General Surgery division, Surgical Service, St. Louis (John Cochran) VAMC

Home phone: 314-455-9482

Pam's cell: 314-809-9634

Cc:

Anthony S. Fauci, M.D.
Director of the U.S. NIAID
U.S. National Institutes of Health
U.S. Dept of Health & Human Services
5601 Fishers Lane, MSC. 9806
Bethesda, MD. 20892-9806
Re: Case # 12276

Phone: 301-496-5717 FAX: 301-402-3573

The Honorable Denis McDonough Secretary, U.S. Department of Veterans Affairs 810 Vermont Ave, NW Washington, DC. 20420 Denis.McDonough@va.gov

Catherine Mitrano, J.D. and Michael R. Hogan, J.D. Office of General Counsel (26)
Designated Agency Ethics Official (DAEO)
810 Vermont Ave, NW
Washington, D.C. 20420

Phone: 202-360-3598

6.0 2021-10-19. How Did We Get Into This Mess?

Dear Mr. President:

Please forgive my forwardness of this cover letter of the documentation I will be presenting to you. Over the last 18 months I have submitted documentation with the U.S. Department of Health and Human Services through the office of the NIAID of the National Institutes of Health, the Office of the Commissioner of the FDA, and many other federal offices including the Office of the President of the United States with little response to my advocacy. As a federal physician of 24 years of service in the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs, it is my duty to bring to your attention that which has collectively been detrimental to the people of the United States of America. While my past focus has been to promote *Passive Immunization* methodologies in the early treatment (<72 hours from diagnosis) of COVID-19 (e.g.: Convalescent Plasma, Convalescent Sera, Monoclonal Antibodies, and Monoclonal Antibody cocktails), the most glaring foundational problem common to our addressing the conoravirus SARS-CoV-2 has been harmful selective transparency. misdirection, **obfuscation**, and lies promoted by U.S. Medicine, U.S. Medical Research, U.S. Pharma, and agencies of the Executive Branch of the Federal Government (e.g.: FDA, NIAID, NIH, CDC, USPHS, VHA of the DVA, etc.). By (1) altering their adherence to their own-stated policies and directives; (2) violating or negating public laws: e.g.: EMTALA, PL-89-97 and The Right to Try Act, PL-115-176; and (3) misinterpreting fundamental immunology concepts; (4) misapplying and ignoring research ethics as proclaimed by the Nuremberg Code, the Helsinki Accords, and the Belmont Report; (5) redefining incorrectly key medical terminology, and (6) misrepresenting the very definitions promoted by the U.S. Department of Health and Human Services: e.g.: Clinical Trials, placebos, EUA, Expanded Access, and the very foundational Congressionally-mandated decrees establishing the FDA (over a century ago), U.S. Medicine and the U.S. Government have synergistically failed the American people!

Attached to this cover letter are multiple aspects of where we, as the U.S.A. in the fight against COVID-19 went wrong. Below is the latest personal example that was presented to my family by my wife purchasing two of the at-home COVID-19 Antigen Self tests: Abbott's BinaxNOW and Quidel's QuickVue. Both contain the following statement (with slight variations):

This product has not been FDA cleared or approved, but has been authorized by the FDA under an Emergency Use Authorization (EUA) for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens...

Except for Remdesivir (VELKURY, NDA #214787, October 22, 2020) and Pfizer's COVID-19 vaccine (COMIRNATY, BL 125742/0, August 23, 2021), all other agents being utilized in the fight of COVID-19 for testing, treatment, and prevention of COVID-19 are under Emergency Use Authorizations (EUAs) which mean they are <u>all</u> "*Investigational*" or in Medical Research

terminology: **Experimental**. We, as a nation, have given out almost 200 million doses of vaccines (**Active Immunization**) under the auspices of **Medical Research experimentation** during this pandemic.—It is no wonder that a large percentage of the American people still refuse to be vaccinated with these "Experimentational Agents." The generic term **Passive Immunization** (Convalescent plasma/sera and monoclonal antibodies) has never been mentioned to the American public even though ~722,000 units of COVID-19 convalescent plasma/sera have been administered over the last 18 months **AT THE WRONG TIME late in the course of the disease!**

Normally, in NIH authorized Clinical Trials and in policies of the FDA, successful completion of a phase 1 trial with regards to <u>safety</u> is met when approximately 20-40 individuals with the disease have had minimal side-effects attributable to the Investigational agent when administered. When efficacy has been demonstrated in Phase 2/3 studies (200-400 individuals) then an agent usually receives FDA approval as a new drug or biologic. Over the last 18 months, hundreds of thousands of these agents of Active and Passive Immunization have been given out by hospitals, infusion centers, and other emergency sites under the auspices of EUAs—Experimental Administrations.

While someone purchasing the OTC tests mentioned above assumes they are <u>screening tests</u> for SARS-CoV-2 antigens in the nares of an individual, **neither meets medical sensitivity significance criteria** for a screening test of 2 standard deviations from the mean (a 95% confidence level): Abbott's BinaxNOW 91.7% sensitivity and Quidel QuickVue At-Home OTC COVID-19 Test of 83.5% sensitivity. **Most of all Mr. President**, while both tests within their packaged directions states that the reagents of the test can be harmful if contacted by an individual, NO WHERE is it stated the legal FDA warning of: KEEP OUT OF REACH OF CHILDREN (21 CFR 369.9) on the packaging. I chose this example because it presents minor lapses of dereliction to duty by the FDA when overall there have been major infractions by the FDA and the NIH.

Throughout the last 18 months, both the FDA and NIH have disregarded or conveniently overlooked the intent, if not the letter-of-the-law, regarding generic adherence and protection of patients' rights (and more specifically, they ignored PL-115-176, The Right to Try Act at every turn) which, in some circumstances, may have been illegal but, in all instances, violated the collective trust of the American people. Collectively, shame on U.S. Medicine and shame on the agencies of the U.S. Department of Health and Human Services! They should all apologize to the U.S. people!

Mr. President: As Dr. Fauci, you, and I grew up in the era of the Roman Catholic Latin Mass, we of U.S. Medicine and the Executive Branch of the U.S. Government should all be beating our breasts and stating: Mea Culpa, Mea Culpa, Mea Maxima Culpa. In the attached documentation, I will try to explain the following:

- 1. My summarization of the natural course of the disease of COVID-19 caused by the coronavirus SARS-CoV-2 including:
 - a. The size of the coronavirus SARS-CoV-2 (50 140 nm) and its implications regarding N95 masks (there are no true antiviral masks and N95 masks inhibit

95% of particles less than 300 nm in size). https://blogs.cdc.gov/niosh-science-blog/2009/10/14/n95/ and https://blogs.cdc.gov/niosh-science-blog/2009/10/14/n95/ and https://www.news-medical.net/health/The-Size-of-SARS-CoV-2-Compared-to-Other-Things.aspx

- b. The implications of the longitudinal graphs of daily new cases of COVID-19 and daily deaths attributable to COVID-19. https://ourworldindata.org/coronavirus Mr. President, did you know that the graphs of the decline of new cases and new deaths represent logarithmic decays that approach zero daily cases and deaths asymptotically?
- c. As we have <u>not</u> until this summer officially treated early (before the cytokine cascade and the bradykinin storm late phase) COVID-19 with passive immunization (monoclonal antibodies), one can mathematically define the natural untreated death rate of COVID-19 patients. The derived equations and graphs from the CDC weekly reports regarding mortality by age groups are the following https://web.archive.org/web/20210217175653/https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge:

$$0-45$$
 years $y = 0.0008x - 0.0103$ R²=0.8254
46 -> 85 years $y = 0.0049x - 0.1216$ R²=0.9972

From 4/2020 to present:

Age Range	Mortality %	Deaths by Age Group
	Infected	100,000 in that Age Group
0 - 17 yrs	0.05%	50
18 - 29 yrs	0.41%	410
30 - 39 yrs	1.19%	1190
40 - 49 yrs	3.10%	3100
50 - 64 yrs	15.47%	15470
65 - 74 yrs	21.63%	21630
75 - 84 yrs	27.06%	27060
\geq 85 yrs	31.09%	31090

- 2. The chronology of what went wrong in the implementation of Passive Immunization from January 2020 to the present.
- 3. It would be my suggestion along with your present COVID-19 White House Task Force members, you might invite to the White House for an educational informational session for you the following physicians and present and former governmental individuals:
 - Francis S. Collins, M.D.; Anthony Fauci, M.D.; Stephen Hahn, M.D.; Janet Woodcock, M.D., Debroah Birx, M.D.; Peter Marx, M.D.; RADM Denise M. Hinton, RN, MS; Michael Joyner, M.D.; Arturo Casadevall, M.D.; Liise-anne Pirofski, M.D.; Jay Epstein, M.D.; Louis M. Katz, M.D.; Leonard Schleifer, M.D.; George Yancopoulos, M.D.; Eric J. Rubin, M.D.; Philip Drazen, M.D.; Howard Bauchner, M.D.; Catherine D. DeAngelis,

M.D.; Jeffrey P. Henderson, M.D.; Bruce Hall, M.D.; Steven L Liebman, M.D., Richard Stone, M.D. as a legal counsel representative: Jeffrey Rosen, J.D. (former acting Attorney General from December 23, 2020 to January 20, 2021.); representatives from the Association of American Blood Banks (AABB) and the American Red Cross, Dawn O'Connell, J.D., Assistant Secretary for Preparedness and Response, DHHS; etc.

- 4. What could be on the agenda for such a meeting:
 - a. A short course in Clinical Immunology regarding the differences between Active and Passive Immunization presented to the President of the United States and how these agents should be utilized synergistically to end the COVID-19 epidemic in the U.S.A.
 - b. Discussion of how to educate the America public and organize infusion centers around the nation for the EARLY administration of Passive Immunization (Convalescent Plasma, Convalescent Sera, Monoclonal Antibodies, and Monoclonal Antibody Cocktails) and Antiviral agents like Remdesivir. Discussion on how to provide the early administration of Passive Immunization throughout the country. Discuss how to mobilized the nation's blood bank to collect and distribute large quantities of COVID-19 convalescent plasma Fresh Frozen plasma (FFP) as was done during WWII administered initially administrated by Charles Drew, M.D., FACS and the by Eleanor Roosevelt. (Today, in one week, literally with 20 donations daily of COVID-19 Convalescent Plasma (CCP) to the >5000 blood banks throughout the U.S.A., 700,000 units of convalescent FFP can be generated. As there are two doses of 200 ml of "high dose" CCP per FFP unit, 1.4 million units per week are possible. If the FFP is "low dose", doubling the volume to a full unit of FFP (400 ml) will double the polyclonal antibodies administered to an individual (e.g.: 2 or 3 x low dose = one high dose unit of CCP) Most of all, on August 23, 2020 using data from approximately 94,000 units administered late in the disease (the wrong time) by the Mayo Clinic/FDA Expanded Access program (compassionate use of which the data should not have been used) the FDA still concluded that "high dose" was better that "low dose" CCP. Mr. President, would it not seem reasonable that "high dose" is better than NO DOSE!
 - c. Mr. President, with the mortality calculations regarding children under the age of 12 derivable from 1c above, **should a school holiday be declared until such time as all the children can be vaccinated?** Right now we are essentially putting our unvaccinated children who have not contracted previously COVID-19—thus, being individually immunity naïve to COVID-19--in harms way.

Using the equation: y = 0.0008x - 0.0103 R²=0.8254

One can calculate the estimated mortality by year per 100,000/infected.

(But by the least square fit equation derived from the CDC data of 0-45 years, the predicted age range mortalities really predicts finite mortality from age 13 years and above)

Age	<u>Mortality %</u>	Deaths by Age Group
	Infected	100,000 in that Age Group
4 yrs	-0.71%	0
5 yrs	-0.63%	0
6 yrs	-0.55%	0
7 yrs	-0.47%	0
8 yrs	-0.39%	0
9 yrs	-0.31%	0
10 yrs	-0.23%	0
11 yrs	-0.15%	0
12 yrs	-0.07%	0
13 yrs	0.01%	10
14 yrs	0.09%	90
15 yrs	0.17%	170
16 yrs	0.25%	250
17 yrs	0.33%	330
18 yrs	0.41%	410
19 yrs	0.49%	490

d. Discussion of the endpoints regarding full approval of all the agents under EUAs that have demonstrated efficacy by appropriate studies (NOT CCP GIVEN LATE IN THE DISEASE AND LACKING AGE STRATIFIED). The FDA can designate as full-fledged drugs and biologics in the treatment of COVID-19 all the present Passive and Active Immunization agents being utilized by shear numbers of administrations of these agents over the last 18 months when they were give early (<72 hours after diagnosis) and when analyzed by age-stratification!

Mr. President, by now you are probably wondering how we got into this mess. Well, frankly, it was a lot of little errors or presentations of selective transparency that cascaded in misleading and misdirecting U.S. Medicine and the US government.

1. The worst error was constructing administration criteria for CCP and Remdesivir at "deaths-door" rather than within 72 hours of diagnosis. On March 24, 2020, the following FDA announcement based on a misinterpretation of a February 2020 Chinese epidemiology paper published in JAMA which never speaks of treatment of COVID-19 was issued that set into motion administration of CCP at the WRONG TIME, initiated a multitude of NIH clinical trials based on the WRONG TIME, and initiate Clinical Practices of administration of CCP at the WRONG TIME that even now have not been rescinded!:

Investigational COVID-19 Convalescent Plasma - Emergency INDs

March 24, 2020

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https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from public health threats including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to doing everything we can to provide timely response efforts to this pandemic and facilitate access to investigational drugs for use in patients with serious or immediately life-threatening COVID-19 infections.

One investigational treatment being explored for COVID-19 involves the use of convalescent plasma collected from recovered COVID-19 patients. It is possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. Although promising, convalescent plasma has not been shown to be effective in every disease studied. It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so. Investigators wishing to study the use of convalescent plasma are encouraged to submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).

Although participation in clinical trials is one way for patients to obtain access to convalescent plasma, these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the expanding COVID-19 outbreak presents, while clinical trials are being conducted, FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency Investigational New Drug Applications (eINDs) for Individual patients under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This does not include the use of COVID-19 convalescent plasma for the prevention of infection.

Healthcare providers interested in the emergency use of investigational COVID-19 convalescent plasma under a single patient emergency IND should consider the following:

COVID 19 Convalescent Plasma

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Additional considerations for donor eligibility should be addressed, as follows:

- · Prior diagnosis of COVID-19 documented by a laboratory test
- · Complete resolution of symptoms at least 14 days prior to donation
- · Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at <a href="https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices/emergency-use-authorizations-
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug-Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

- . Eligible patients for use under expanded access provisions:
 - Must have laboratory confirmed COVID-19
 - Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or
 - multiple organ dysfunction or failure
 - Must provide informed consent

How to obtain authorization for use of COVID-19 convalescent plasma

- For request that are not highly time sensitive (response from FDA provided within 4 to 8 hours), the requesting
 physician may contact FDA by completing form 3926 (https://www.fda.gov/media/98616/download) and submitting the
 form by email to Covid-19@FDA.HHS.gov.
 - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements of 21 CFR 312.305 and 312.310.
 - The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
 - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.
 - FDA will review the request and, upon approval, FDA will send the requesting physician a confirmatory email that includes the emergency IND number.
- In the event of an emergency that is highly time sensitive (response required in less than 4 hours) or where the
 provider is unable to complete and submit form 3926 due to extenuating circumstances, the provider may contact
 FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
 - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 15 working days of FDA's authorization of the use.

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

⁵ 1Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72†314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Content current as of: 03/24/2020

A British Medical Journal article: https://www.bmj.com/content/bmj/368/bmj.m1256.full.pdf of March 26, 2020 documented for the world this announcement with it attached three references:

- 1 FDA. Investigational covid-19 convalescent plasma—emergency INDs.

 https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber-investigational-covid-19-convalescent-plasma-emergency-inds (When one attempts to use the Wayback machine to find this site, the response is Wayback Machine has not archived that URL.)
- Hixenbaugh M. FDA will allow doctors to treat critically ill coronavirus patients with flood from survivors. NBC News 2020 Mar 24.

 www.nbcnews.com/news/us-news.com/news/us-news/fda-will-allow-doctors-treat-critically-ill-coronavirus-patients-blood-n1167831 which contains the hyperlink: emergency protocols approved by the FDA which directs to: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma (the February 11, 2021 which is the Wayback Machine first "captured". ****Need to research this more as previous with the Wayback Machine pointed to April 8, 2020)
- Palca J. FDA expedites treatment of seriously ill covid-19 patients with experimental plasma. National Public Radio, 24 Mar 2020.

 www.npr.org/sections/coronavirus-live-updates/2020/03/24/820939536/fda-expedite-treatment-of-seriously-ill-covid-19-patients-with-experimental-plasma which contains the hyperlink: emergency protocols approved by the FDA which directs to: www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma (the February 11, 2021 which is the Wayback Machine first "captured". ****Need to research this more as previous with the Wayback Machine pointed to April 8, 2020)

Reference 1 points to a URL that no longer exists and the other two in the body of the article points to the URL: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drugapplications-inds-cber-regulated-products/recommendations-investigational-covid-19convalescent-plasma of February 11, 2021. Previously, if one copied to this URL into the Wayback Machine of the Internet Archive, the initial document in April 2020 which was an expost facto document of April 8, 2020. This represents Now missing "reference" regarding justification for the criteria incorrectly attributed to the JAMA article of Wu Z, McGoonan JM...(see above)" of the FDA March 24, 2020 announcement. The Incorrect "Eligibility Criteria" criteria was the limiting factor regarding administration of CCP and Remdesivir until September 2, 2020 and August 28, 2020, respectively. The FDA was so "quiet" about these corrections that the VHA issued in November 2020 administration inclusion regarding Remdesivir which was (under the drug name VELKURY) as October 22, 2020 the only FDA fully-approved antiviral (NDA #214787) in the (early) treatment of COVID-19. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf THE WRONG ADMINISTRATION INCLUSION CRITERIA remains the official criteria of the VHA listed on the internet to this day.

https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf

2. Mr. President, I would suggest you issue an Executive Order banning the present practice across the Executive Branch of the U.S. Government of "Overwriting" official documents. You could then mandate in the Executive Order the reinstatement of the practice that all official documents, policies, directives, and memos of all Departments of the Executive Branch of the U.S. Government document on the face sheet the previous document, policy, directive, and/or memo the present version is replacing the previous replacement document should be recorded in the new version so the new version can be compared by the rescinded version—that is true transparency. At present, if the replacement document is overwritten electronically and the URL is maintained, the replaced/rescinded document can be located, if the URL has not been changed, by utilizing the "Wayback Machine" of the Internet Archive (San Francisco, CA).

---Stopped at this Point----2021-10-20

20.0 7.0 2021-09-19 Timeline of U.S. Government Regarding Passive Immunization and the Discrediting of COVID-19 Convalescent Plasma

Dear Mr. President:

Please excuse my forwardness in submitting this cover letter to you but it is of major importance and my duty as a federal physician to appraise you of this. As Dr. Birx said in her interview with Margaret Brennan on face the nation on January 24, 2021, this may never come out in her lifetime. The bottom line is that US medicine and the executive branch of the federal government in March 2020, abandoned the America people by NOT offering **Passive Immunization** as the immediately available treatment of COVID-19, future synergistic treatment with **Active Immunization** in all that contract COVID-19 after vaccination, and a prophylaxis for high-exposure individuals like healthcare workers, first responders, grocery clerks, immune suppressed individuals and everyone else. The timeline of the failure of U.S. Medicine, U.S. Research, and the U.S. Government regarding **Passive Immunization** is as follows:

- 1. On March 3/2/2020, leaders of Pharma, the FDA, the NIH, etc. met with President Trump and failed to make the distinction of **Active Immunization versus Passive Immunization.** https://www.youtube.com/watch?v=31i6p_stzW8
- 2. President Trump declared an emergency on March 13, 2020. https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/
- 3. Secretary Azar on March 13, 2020 suspended parts of EMTALA retroactive to March 1, 2020. https://www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx
- China sends medical team to Italy to set up 50 blood collection centers to help in treatment of COVID-19. https://www.chinadaily.com.cn/a/202003/14/WS5e6bd352a31012821727f096.html
- 5. On March 19, 2020, Johns Hopkins Bloomber School of Public Health carries story of China offering to Italy 90 tons of COVID-19 Convalescent Plasma (~500,000 doses). https://www.globalhealthnow.org/2020-03/covid-19s-stop-gap-solution-until-vaccines-and-antivirals-are-ready
- 6. On March 24, 2020, **FDA Failure because** instead of the FDA declaring **Passive Immunization** synergistic with future vaccination (active immunization--vaccination) and declaring convalescent plasma (a Nobel Prizing winning passive immunization, 1901) a biosimilar biologic to e.g.: rabies vaccine, RhoGAM gamma globulin, IVIG, tetanus hyper immune globulin, etc., the FDA **declared COVID-19 convalescent plasma** <u>investigational</u>. (i.e.: **EXPERIMENTAL**)

 https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf
- 7. In order to make convalescent plasma immediately available the FDA authorized **expanded access (COMPASSIONATE USE)** through six programs in the United States WITH most visible that through the Mayo Clinic in which over >2700 hospitals would participate.
 - https://web.archive.org/web/20200404010134/https:/www.uscovidplasma.org/ By the definitions of the NIH and FDA "Expanded Access" is "Compassion Use" (DATA NOT

- <u>AVAILABLE</u> TO BE USED FOR CLINICAL TRIALS) which means that any data from the administration of over 94,000 doses by the Mayo Clinic from March 24, 2020 to EUA of August 23, 2020 should not have been used as data for research studies. (The vast majority of <u>CCP administrations were given late in the disease at the WRONG TIME.)</u>
- 8. On March 24, 2020 the FDA announced inclusion criteria for administration of COVID-19 convalescent plasma which was wrong giving it only when the patients were on death's door with the FDA referencing their misinterpretation of an Chinese epidemiology paper published in February 2020. (The FDA removed the reference in all subsequent documentations and failed to tell the American public they were administering CCP at the WRONG time. The FDA quietly removed the WRONG inclusive criteria from all subsequent documentation on September 2, 2020.) Passive immunization has only been shown to be most successful in previous epidemics when given within the first 72 hours of diagnosis—NOT at death's door!

 https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20 %20FDA.pdf
- 9. For the last 18 months the FDA has made all the agents of passive Immunization experimental (Investigational) by issuing EUAs. In so doing they violated the intent (and really the letter of the law) of PL-115-176, the Right to Try Law https://www.govinfo.gov/content/pkg/PLAW-115publ176/pdf/PLAW-115publ176.pdf in limiting the ability of patients to request Passive Immunization agents —thus, abandoning / withholding treatment of the American people within 72 hours of contracting COVID-19.
- 10. CCP was issued its first EUA on August 23, 2020 while still under the restrictive late-in-the-disease inclusion criteria of March 24, 2020. The FDA quietly rescinded this wrong inclusion criteria on September 2, 2020 and then did not notify the American public. (The FDA also quietly rescinded the same inappropriate inclusion criteria regarding Remdesivir on August 28, 2020.). President Trump in the first 2 minutes of the White House Press Conference insulted China by referring to the coronavirus SARS-CoV-2 virus as the CHINA virus. (China stopped their epidemic by quarantine and liberal use of CCP. How does one know this?--In March 2020, China sent 15 medical personnel to Italy to assist in the development of CCP infusion centers and China offered 90 tons of surplus CCP to the Italians.)
- 11. October 2, 2020 President Trump was diagnosed with COVID-19, and within four hours President Trump was given Regeneron monoclonal antibody cocktail and within 18 hours began Remdesivir infusions. Subsequently, it is documented that former Governor Christie, former Mayor Giuliani, and former HUD Secretary Dr. Ben Carson received at least monoclonal antibodies. While every person in the United States who turned positive for COVID-19 should have been eligible for early administration of this combination of monoclonal antibodies and Remdesivir, it was concealed in plain sight from the American people by agencies of the Executive Branch of the Federal Government by not announcing its significance formally to the American people.
- 12. In November 2020 the VA issued the incorrect timely--administration inclusion criteria for Remdesiver (Velkury), which had been approved as a prescription drug on October 22, 2020 by the FDA. The VHA still lists this incorrect administration criteria continuing to this day on the Internet to this day. At the time, I was in e-mail communications with

- VHA Chief Medical Execuative, Richard Stone, M.D., (really VHA Under Secretary of Health although I am not sure he was approved by Congress) and *The New England Journal of Medicine*.
- 13. On January 6, 2021, *The New England Journal of Medicine* published the **only prospective, randomized, placebo-controlled, appropriately timed (<72 hours from diagnosis administration), age-stratified CCP administrated article** for the last 18 months. This "landmark" article definitively demonstrated that when CCP was administered early (<72 hours from time of diagnosis) and compared with placebo in 70 year old patients, the decrease in hospitalization was significant (p< 0.03) and the morality was halved (CCP=2 vs. placebo=4) but did not reach significance as the study was too small.
- 14. On January 24, 2021, Dr. Birk's was interviewed by Margaret Brennan on *Face the Nation*. https://www.youtube.com/watch?v=odklJGnhvhU
- 15. On February 1, 2021, I e-mailed the FDA, NIH, *The New England Journal of Medicine*, and many pertinent persons (*reducio-ad-absurdum*) pointing out Dr. Birk's plea.
- 16. On February 4, 2021, the chief scientist of the FDA, RADM Denise Hinton issued a new EUA for Convalescent Plasma (*vis-a-vis* coinciding within 48 hours of my letter to Dr. Birx).
- 17. Within 24 hours, Peter Marks, M.D., Chief of the Biologic Division of the FDA is quoted in the WSJ with conflicting remarks about convalescent plasma. He then issues an official statement from the FDA and in an interview three weeks later praising CCP.
- 18. In the NEJM on February 18, 2021, Dr. Katz Acting Director of the Mississippi Valley Blood Authority (now renamed ImpactLife) prints a three page light-hearted, obfuscating editorial entitled: (A Little) clarity on convalescent plasma for COVID-19.
- 19. In February 2021, BARDA announces it will defund CCP throughout the nation.
- 20. March 8, 2021, ImpactLife to phase out CCP donations (~120 hospitals in the Midwest)⁴⁸⁴
- 21. The NIH quotes an underpowered study (results not published) regarding a non-age-stratified placebo-controlled ER study on CCP administration that was closed early because they could not recruit even patient's for the placebo study.
- 22. March 10, 2021: Convalescent Plasma Strikes Out as COVID-19 Treatment. https://www.npr.org/sections/health-shots/2021/03/10/975365309/convalescent-plasma-strikes-out-as-covid-19-treatment
- 23. April 21, 2021: NIH COVID-19 Treatment Guidelines panel recommends against COVID-19 Convalescent Plasma.

 https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/convalescent-plasma/
- 24. Regeneron teams up with ROCHE International to market REG-CoV-2 (monoclonal cocktail to the world). (ROCHE is selling REG-CoV-2 to Indian hospitals for 50,000 Repees (~\$800) for those that can afford it to be given early in the course of the disease. On-the-street it is referred to as the "Trump cocktail")
- ---this is incomplete but will be submitted as it is an extensive timeline on how COVID-19 Convalecent Plasma was discredited, 10/20/2021

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21.0 8.0 2021-09-12 Confirmation of NIAID file: Case # 12276; Brief COVID-19 Pathophysiology Overview; and Dr. Fauci's Similar Monoclonal Antibody Speeches of 4/2018 in *The New England Journal of Medicine* (2 years before the World Health Organization declared COVID-19 a Pandemic) and the 8/24/2021 White House Press Briefing with a Slide Show narrated by Dr. Fauci

Dear Mr. President:

Please excuse my forwardness in contacting you today; but, as a VA Federal Physician who has attempted to communicate with *The White House*, the NIAID of the NIH, and the office of the commissioner of the FDA since early April 2020, it is my duty to submit this Report of Contact to you regarding a phone call I received on my VA office phone (314-652-4100 ext 54463) on Monday, August 30, 2021, from "Meg" of the Communications Office of the U.S. National Institutes of Health (NIH), National Institute of Allergy and Infection Diseases (NIAID). "Meg" stated she was responding at the request of Kara Harris regarding my phone call on that day that I had placed on the voicemail of Kara M. Harris, MPH on August 30, 2021, in regards to Dr. Fauci's White House slideshow of August 24, 2021. (On June 10, 2020, Ms Harris had responded to me in writing—assigning my correspondence and documentation the NIAID Case file # 12276--at the request of Dr. Fauci. [Ms. Harris is the Section Chief for Controlled Correspondence and Public Inquiries, Legislative Affairs and Correspondence Management Branch, Office of Communication and Government Relations, National Institute of Allergy and Infectious Diseases, National Institutes of Health]). "Meg" assured me that my concerns had been forwarded to divisions of the NIAID that could address them. She then patiently—without interruption-- listened to me voice my concerns and advocacy regarding *Passive Immunization* for at least 20 minutes. As I drew to the end of my thesis, she stated that the problem was mainly with the FDA. Mr. President, this is an example of the silo-thinking that is pervasive today in our collective mindset. I immediately challenged "Meg" with the fact that the NIH and the FDA are both agencies of the U.S. Department of Health and Human Services. With this, "Meg" stated that she had to go but she assured me that the NIAID still had my submissions.—I presume in the file: NIAID case # 12276.

As a General Surgeon of the VA-University Affiliation of 1946 (PL79-293) cumulatively for almost a quarter of a century, it has always been my duty as a Federal Physician in the Veterans Health Administration of the U.S. Department of Veterans Affairs to responsibly report my concerns to my superiors. For the last 18 months, I have submitted to *The White House*, the agencies of the U.S. Department of Health and Human Services, the U.S. Department of Veterans Affairs, and the U.S. Copyright Office of the Library of Congress--for historic documentation—my communications in support of the early Passive Immunization treatment (usually <72 hours) of COVID-19 -- not just prevention. As such, early treatment of COVID-19 has been available for the vast majority of this U.S.A. epidemic in the form of *Passive* Immunization (e.g.: COVID-19 Convalescent Plasma and Sera and, by the summer of 2020, monoclonal antibodies and antibody cocktails). While the FDA, the NIH, and the VA have tacitly responded to my submissions with form letters and emails, dismissive correspondence, or just plain silence, as a VA Federal Physician I realized that my interaction with these entities should be recorded for history. I will submit this present correspondence and documentation today with you to the NIH, NIAID Case file #12276 and, as with the previous three series of documents, to the U.S. Copyright Office of the Library of Congress in a plea for appropriate

application with *Passive Immunization* of the <u>early treatment of COVID-19 disease</u> in addressing the early pathophysiology of the SAR-CoV-2 virus.

The pathophysiology of the SARS-CoV-2 virus and subsequent disease process can be categorized in two phases: (1) the early viremic phase of COVID-19 infection and viremia and (2) the later phase of bilateral pneumonia resultant from the cytokine cascade and the bradykinin storm. The late phase involves the individual's systemic response and pathologic changes with resultant morbidity and mortality. As Dr. Fauci emphasized on August 24, 2021, monoclonal antibodies (one of the treatments of *Passive Immunization*) have been a much underutilized interventions—but all of *Passive Immunization* agents have been (1) underutilized or administered at the wrong time, (2) considered experimental under EUAs thus preventing the individual American's right-to-try under PL-115-176, and (3) by research obfuscation and distraction utilizing "Expanded Access" (which is really is compassionate use of whose data is not available for Medical Research data collection by FDA/NIH definitions). Passive *Immunization* when given at the appropriate early administrative time in some form has been available throughout the last 18 months but has been discredited and downplayed for various reasons by the FDA, the NIH, and the pharmaceutical industry ("operation warp-speed"). My previous submissions regarding *Passive Immunization*, [e.g. COVID-19 Convalescent Plasma (CCP) and Sera (both of which are polyclonal antibodies); monoclonal antibodies; and monoclonal antibody cocktails] are as follows:

- Andrus CH: *Time*: The Crucial Independent Variable of the COVID-19 Pandemic, U.S. Copyright Office, Library of Congress, 2020-06-08, Txu002199029.
 <a href="https://web.archive.org/web/20210904014401/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=9&ti=1%2C9&Search_Arg=Andrus+Charles+H&Search_Code=NALL&CNT=25&PID=DvTGOW_Qvd_foYxTFrVcdewL3ktMCwz&SEQ=20210425193720&SID=1
- Andrus CH: The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma. U.S. Copyright Office, 2020-07-22, TXu002214049.
 https://web.archive.org/web/20210904020833/https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=6&ti=1%2C6&Search_Arg=andrus+charles+h&Search_Code=N_ALL&CNT=25&PID=cXfFuGrmHQvLVlLvfNNt7Yjwh73ImgQ&SEQ=202105120814_28&SID=1
- 3. Andrus CH: 1 Dear Mr President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. U.S. Copyright Office, 2020-11-18, TXu002232947. https://web.archive.org/web/20210904021628/https://cocatalog.loc.gov/cgibin/Pwebrecon.cgi?v1=3&ti=1%2C3&Search_Arg=andrus+charles+h&Search_Code=N_ALL&CNT=25&PID=py6zcjaddPxEbahiUXXmsV0vRNwjXMy&SEQ=202105120817_35&SID=2

When I saw *The White House* presentation by Dr. Fauci of August 24, 2021, on YouTube regarding monoclonal antibodies https://www.youtube.com/watch?v=AZNP05w2cxU (YouTube minutes 10:30 – 15:25), I immediately realized it was my duty to respond to you regarding the

unmentioned medical assumptions in that discussion that are crucial for the implementation of <u>early</u> treatment TO ALL (within 72 hours of diagnosis) of COVID-19 with *Passive Immunization*—that is, providing exogenous antibodies against SARS-CoV-2 to individuals both prophylactically and early-in-the-treatment of the infection/viremia phase of COVID-19.

(Transcript: https://www.whitehouse.gov/briefing-room/press-briefings/2021/08/24/press-briefing-by-white-house-covid-19-response-team-and-public-health-officials-51/)

DR. FAUCI: Thank you very much, Dr. Walensky. I'd like to spend the next couple of minutes in addressing a much-underutilized intervention for COVID-19, and that is the use of monoclonal antibodies for the treatment and prevention of SARS-CoV-2 infection and COVID-19 disease.

Next slide

For those not totally familiar with this, monoclonal antibody is an antibody that's produced by a single clone of B cells or a cell line, and consists of identical antibody molecules that can actually be produced in the in-vitro situation in unlimited quantities.

Next slide.

If you look at the virion on the upper-left part of the slide and you look up the blown-up spike protein — the red molecule on the right upper panel — when you talk about polyclonal antibodies, which result from infection or vaccination, it's a group of antibodies against every aspect of the spike protein, which is the good news. However, the concentration and the affinity of those antibodies can be markedly improved if you get a single cloned antibody — hence the word "monoclonal" — that's against the very specific part of the spike protein that can have a major effect in prevention and treatment.

Next slide.

So, let's look at what we have. We have three anti-SARS-CoV-2 monoclonal antibody products that have currently had Emergency Use Authorization from the FDA. And the EUAs here are for adults and children 12 years of age and older who weigh at least 88 pounds.

There are three of them. There's the Lilly product — the bamlanivimab plus etesevimab. There's the Regeneron project — product, referred to as REGEN-COV. And then there's the GSK and Vir product. Each of these products targets the spike protein of SARS-CoV-2.

Next slide.

So, you can do an indication for these antibodies that are twofold. The first is to treat infection with SARS-CoV-2.

Next slide.

And in this regard, clinical trials have demonstrated that early treatment with anti-SARS-CoV-2 monoclonal antibodies can reduce the risk of COVID-19 hospitalization or death by 70 to 85 percent.

It is important to emphasize that this must be done early in infection and not wait, of course, until a person is sick enough to be hospitalized. That's when you get the best effect.

And again, being an underutilized intervention, we want people out there, including physicians, as well as potential patients, to realize the advantage of this very effective way of treating early infection.

Next slide.

Now, if you look at the people who should benefit from this, this is a list from the FDA and the NIH treatment guidelines about all of the people who may have significant benefit from this type of therapy if given early in their infection.

I'm not going to go through each and every one of them, but as you can see, there are a number of conditions on this slide that could benefit from the monoclonal antibody treatment after infection.

Next slide.

But there's also the benefit of prevention using monoclonal antibodies.

Next slide.

And we know now that the FDA, just a couple of weeks ago, authorized the Regeneron monoclonal antibody for post-

exposure prophylaxis, namely for the prevention of COVID-19 after someone has been exposed to a documented case of SARS-CoV-2.

And even now — and I won't show the data because of lack of time — there are now studies in pre-exposure prophylaxis, as well as other studies in treatment.

So, I'll have on the last slide — next slide — the treatment guidelines panel. We can give you all the information, and it's accessible on the website shown here. And for physicians, patients, and others who want to know how you can get monoclonal antibodies administered, this is the call center and this is the online way to approach it.

So, bottom line is: This is a very effective intervention for COVID-19. It is underutilized, and we recommend strongly that we utilize this to its fullest.

Three years ago, Dr. Fauci was the senior author of the *New England Journal of Medicine* (NEJM) article: Marston HD, Paules C, Fauci AS: Monoclonal antibodies for emerging infectious diseases – Borrowing from history. N Engl J Med 2018 Apr 19; 378 (16): 1469 – 1472: https://www.nejm.org/doi/pdf/10.1056/NEJMp1802256?articleTools=true. In the supplemental NEJM Managing Editor's interview of Dr. Fauci regarding this publication, Dr. Fauci laid out a factually similar discussion and advocacy for early treatment of novel viruses with monoclonal antibodies <u>8 months before</u> SARS-CoV-2 was even detected, identified, or in the consciousness of humanity!:

Morrissey S, Fauci A: Interview with Dr. Anthony Fauci on the use of monoclonal antibodies in the context of emerging infectious diseases. Supplement to the N Engl J Med 2018; 378: 1469-1472. (Mr. President, please listen to this five minute interview after reviewing Dr. Fauci's youtube slide presentation and discussion of August 24, 2021 White House Press Conference listed above—the hyperlink for the 2018 Morrisey-Fauci interview is: <a href="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMp1802256&area="https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056%2FNEJMdo0024

Dr. Morrissey:

Although there is a long history of plasma derived treatments for several pathogens, only a handful of antibody therapies have been licensed for infectious diseases. But recent advances in the development of monoclonal antibodies could have important implications for our response to infectious disease outbreaks. I'm Stephen Morrissey, Managing Editor of the New England Journal of Medicine, and I am talking with Anthony Fauci, Director of the National Institute of Allergy and Infectious diseases. Dr. Fauci has coauthored a prospective article about the promise of monoclonal antibodies for rapid intervention during infectious disease outbreaks. Dr. Fauci: What are the primary benefits of using monoclonal antibodies for prevention and treatment infectious diseases? What advantages do they have over current approaches?

Dr. Fauci:

Well, one of the things that got us to be very interested in that is just that potential advantage. Namely, that when you have to respond, for example, to an unexpected outbreak of an infectious disease, one of the major tools against that to control it or hopefully eliminate it is development of a safe and effective vaccine. The problem with that is that the time that it takes, even when you put it on a rapid pace, the time that it takes to get a vaccine that you show to be safe and effective often falls behind and lags dramatically behind the actual outbreak itself. Whereas if you can with our techniques that we have right now which of greatly improved over the past several years to isolate and develop monoclonal antibody specific to the agent in question--you can use it much more rapidly. Obviously, there's the issue of being able to scale up, but you get a monoclonal antibody in hand soon after you're confronted with an outbreak has a major advantage over the long time-honored but nonetheless rather drawn-out process of developing a vaccine.

Dr. Morrissey:

You write in your article that several antibody therapies have been licensed for infectious diseases. What have researchers learned from the development of those therapies and for more recent attempts to create monoclonal antibodies against—say-- Ebola or Zika?

Dr. Fauci:

Well, for example, a classic monoclonal antibody for prophylaxis against Respiratory Syncytial Virus has been developed with considerable success. We began thinking very intensively about this just literally over the past few years when we in rapid succession had to confront both the Ebola outbreak followed by the Zika outbreak. And it became very clear that during the Ebola outbreak that there were monoclonal antibodies in the form of ZMapp that was able to actually have an impact even though we did not have the opportunity of doing a very large clinical trial. We did show that there was clearly a tendency towards a benefit of this cocktail of three mouse human chimeric antibodies against Ebola, that we felt that this particular approach if perfected both in the development and scale-up of these antibodies might have an important role in future outbreaks. So, we're thinking that this is going to be something, and including for example influenza, so there have been now a couple of monoclonal antibodies that have been made against influenza. And when you think in terms of a threat of a pandemic influenza and you would want to get an antibody that would be effective in neutralizing a brand new virus well before the time it takes to develop the vaccine, here again is something that we're going to be pursuing and are pursuing at the present time.

Dr. Morrissey:

So how do you envision that process of developing new antibody therapies during an outbreak?

Dr. Fauci:

There a couple of ways of doing that. Probably the easiest way, because the technology now is so sophisticated, is to get an individual who has been infected with whatever pathogen is the one behind the outbreak. And because of the ability now to clone the B cells from the B cell repertoire and essentially fish out—and, truly metaphorically fishing-out the right B cell clones that have the specificity that you are thinking about and wanting to develop and immediately get those to be cloned, sequenced, and then the development of a high through-put process to give you monoclonal antibodies. That's something that was unheard of years ago—literally unheard of where you can actually probe and interrogate the B cell repertoire and the B cell lineage of a person who has recovered from the infection in question; and use those B cells as the source of the monoclonal antibody in question. And that's something that could be done immediately, and from the standpoint of the process of it, to be done very rapidly. So you can envision an outbreak where you have right-away, the sentinel people you have clearly getting sick from the pathogen you have in question and as they recover you just draw some blood from them and you can pull out with the techniques we have a variety of B cell clones that have various specificities and then you can test in vitro what is the best, what has the highest affinity, what is the most specific, what are the epitopes involved, and then start using them for both diagnosis, prophylaxis, and for treatment.

Dr. Morrissey

You talk in your article about the current high cost of production and complexity of administration of these monoclonal antibodies. So how great a limitation is that and do you foresee a time when those issues will be less of a barrier than they are now?

Dr. Fauci:

Well, that's a great question, and I'd have to answer totally, honestly—that it is a barrier that is substantial right now at present. But as we've done with so many other things that we've been able, we in the field, not me personally, but we in the field have been able to develop over years--is that once you get the first step namely the specificity, the effectiveness of a particular antibody, then you work on the development of scale-up. But the idea of scaling up at a reasonable cost where these antibodies can be used widely is a challenge. But I do believe that as we get better and better at it as we have with other technologies that have started off to be very cumbersome and very expensive, I believe over time when there is accelerated interest in this approach which I believe there will be that we will be able to overcome that barrier of the ability to produce at a high degree.

Dr. Morrissey:

In your article, you describe three indications for monoclonal antibodies: the treatment of infected individuals, targeted prophylaxis to protect high-risk individuals, and targeted prophylaxis to interrupt transmission in populations at average risk. So which of these strategies do you think has the most potential to halt the spread of an epidemic?

Dr. Fauci:

Well, clearly if you are talking about halting the spread of an epidemic, the last two that you mentioned because the first one is the treatment of an infected individual. Now obviously you can say well treatment will turn out to be prevention because if you treat a particular person they may not transmit it to another; but I think the much more efficient way of preventing the expansion of an outbreak is the targeted prophylaxis either directly at high risk individuals or even at a population level to prophylaxis and interrupt transmission in people who are at average risk and that is really what we talk about in interrupting the chain of transmission. So, if you have an influenza outbreak, you may be able to use this as prophylaxis before you get a vaccine that is available to essentially have a more population-based prevention.

So, I believe the high risk individuals that are targeted for prophylaxis is going to be a very important way to interrupt certain outbreaks regardless of what the source of that outbreak is.

Dr. Morrissev

Finally, what will it take to increase our interest in our investment in the use of monoclonal antibodies for infectious diseases? What, for example, is NIAID doing?

Dr Fauci

Let me answer your question broadly, then I will get back to the specific of what we are doing. Really nothing succeeds like success as they say. Once you start demonstrating the effectiveness of this approach in different outbreaks—and we have seen inklings of this with the ZMapp approach to Ebola with some of the monoclonal antibodies—all-be-it in the animal models with Zika, they worked very well in the animal models to prevent the transmission of the virus to a fetus in an animal model; and thus prevented the congenital defects in this animal model. I believe that when we get to the point of testing it in humans, under these circumstances, we will see similar success. So, that is what I mean by nothing succeeds like success once you have a few examples of successful application of this particular approach. You are going to get a lot more interest in it. What we at NIH are doing is what we do most of the time is these types of approaches; and that is, to do the basic and clinical research to get this developmental process to be quick and to be effective. We done that and it ranges all the way from the fundamental basic research on B cell lineage—that really led to the ability to develop monoclonal antibodies at a high degrees of specificity and the high degree of ability to neutralize whatever a particular pathogen you have in question. So, the NIH 's job will be what we have been doing all a long, is the fundamental basis to give clinical research leading to the application of these types of interventions.

Dr. Morrissey: Thank you, Dr. Fauci.

Mr. President, this present imploration has become the distillation of my multiple previous failed attempts to construct a cogent missive and communicate to the U.S. Government and the American people the significance of *Passive Immunization*. I will attach the drafts of this present correspondence after this letter as they address many associated aspects but they lack the cohesiveness, conciseness, and completeness of this submission. As Shakespeare has stated: "...The play's the thing / Wherein I'll catch the conscience of the King." To catch the conscience of American Medicine, the Federal Government, and the American people in the coming dissertation, I will employ the vehicle that all American physicians and surgeons of the previous generations of the last century are most accustomed to: The Socratic Method of: *At-the-Bedside-Teaching of Drs. Osler and Halsted.* I will first provide you: (1) a short summary, as I see it, of the clinical pathophysiology of the disease caused by SARS-CoV-2: that is, COVID-19; and then, employing the transcript of Dr. Fauci's slide show of August 24, 2021 White House press briefing, I will generate a series of relevant questions and answers regarding the Treatment and Prevention of COVID-19 symptomatology *at-the-Bedside of Americans suffering the ravages of COVID-19*.

1.) An abbreviated Pathophysiology regarding the SARS-CoV-2 Coronavirus that causes COVID-19:

a. **SAR-CoV-2 virus is a respiratory transmitted RNA coronavirus of ~80 – 120 nm in size.** As such, N-95 masks obstruct all but 5% of passage of particles that are less than 300 nm. All other paper, cloth, etc. masks are much more porous the than N-95 mask. Mr. President, if your federally-issued mask is as effective as my federally-issued VA mask, you should be able during daylight hours to hold the mask up against a window pane of the Oval Office and with gentle stretch on the ear lobe holders, see pinholes of light through it. I can read AV and see the VA seal backwards when I do this—can you see the seal of the United States of

America through your mask? So, then, why wear masks?—Because, wearing the mask is the epitomization of the most noble human act for which we should all strive: *The Golden Rule*--Do unto others as you would wish others do unto you. In short, while a mask provides some protection to the individual wearer, it provides much more protection to the others in the room from the masked wearer's nasal-sneezed-snot and coughed-phlegm.

- b. Once SARS-CoV-2 is in the individual's nose, the mucus and the IgA antibody of the nasal mucosa will address this point of entry. Unfortunately, if the individual's nasopharynx has never developed IgA (the individual is naïve to SARS-CoV-2 never having been exposed), the SAR-CoV-2 virus will not be degraded and the individual will test PCR positive. If there is IgA antibody present in the mucus of the nasopharynx (require ~5 days after initial exposure to reach ~90% of maximum titer), the SAR-CoV-2 may be inhibited or inactivated but the individual will still test PCR positive.
- c. Once the SAR-CoV-2 virus enters the lungs, it can enter the pneumatocytes (and other cells) of the lungs via the spike protein via the ACE receptor site.
- d. During the viremic phase (early phase) of COVID-19, the SAR-CoV-2 virus replicates. It is at this phase where *Passive Immunization* and *Antivirals* should be most effective in addressing viremia in the SARS-CoV-2 immunologicallynaïve individual. During the viremic phase, the individual's immunologic response is stimulated to produce IgM to IgG—but, it takes on average 14 days to reach 70% of the total IgG in the immunologically-naïve individual.
- e. Once the patient has developed the bilateral pneumonia, the patient's **cytokine pathway will have been activated which can be a double-edged sword**—both, combating **SARS-CoV-2** but also potentially causing cytotoxic effects on the individual's cytokine secreting cells. This is where the anti-inflammatory steroid drugs like dexamethasone should be most effective.
- f. The SARS-CoV-2 enters the cells via the ACE receptors, it seems to block the breakdown mechanism of bradykinin. The accumulation of bradykinin is additive to the cytokine detrimental effect thus encouraging/transitioning into the late phase of COVID-19. As both the cytokine cascade and the bradykinin storm become increasingly significant independent to the viremia over time, *Passive Immunization* and *Antivirals* become decreasingly effective. THERE IS NO TREATMENT AT PRESENT TIME REGARDING INCREASED CIRCULATING BRADYKININ. Ask Dr. Fauci to discuss the events seen resultant from the ACE-inhibitors in some individuals of a drug-induced chronic cough and angioedema due to impaired bradykinin destruction.

2.) <u>Discussion of the timeline of Treatments and Prevention of COVID-19:</u>

a. Treatments and the timeline:

- i. January 2020: BARDA funds R&D of Regeneron COVID-19 monoclonal antibiotics in January 2020
- ii. February 2020: Epidemiology study published in JAMA reports on 72,000 Chinese who contracted COVID-19 itemizing symptoms. The report does not mention any treatment but will be used as justification of Eligibility criteria in some form from March 24, 2020 to September 2, 2020. Continued misinterpretation of this article is continued to the present by the VHA.
- iii. March 3, 2020: Pharma meets with representatives of the NIH, the FDA, and the President discussing vaccines and monoclonal antibodies. President Trump misinterprets monoclonal antibodies with vaccines.
- iv. March 13, 2020: President Trump declares emergency
- v. March 17, 2020: HHS Secretary Azar suspends parts of EMTALA retroactive to March 1, 2020.
- vi. March 24, 2020: FDA declares COVID-19 Convalescent Plasma *Investigational* instead of *Biosimilar*. The FDA misinterprets the symptoms reported in the JAMA article of February 2020 as Eligibility Criteria for the administration of CCP at the pathology extremes of COVID-19 instead of within <72 hours of diagnosis.
- vii. April 8, 2020: The FDA formalizes directions to the Industry codifying the wrong time for CCP administration use. The FDA will rescind the severe Eligibility Criteria on September 2, 2020 but not announce it to the nation. The FDA will initiate the Mayo Clinic Expanded Access program for CCP to be given at the wrong time. In FDA and NIH terminology, "Expanded Access" is equivalent to "Compassionate Use" which disqualifies any data collection. >94,000 doses CCP will be administered through the Mayo Clinic/FDA Expanded Access between April 8, 2020 to August 23, 2020. After Ebola, the World Health Organization and the Institute of Medicine warned the U.S. Medicine to avoid such use of Expanded Access as inappropriate and anti-research protocol.
- viii. May 1, 2020: Dr. Fauci announced the EUA for Remdesivir.

Please note the above timeline was never completed in this draft and that this timeline is elaborated upon in: 5.0 2021-09-19 Timeline of U.S. Government Regarding Passive Immunization and the Discrediting of COVID-19 Convalescent Plasma

DR. FAUCI: Thank you very much, Dr. Walensky. I'd like to spend the next couple of minutes in addressing a much-underutilized intervention for COVID-19, and that is the use of monoclonal antibodies for the treatment and prevention of SARS-CoV-2 infection and COVID-19 disease.

Next slide.

For those not totally familiar with this, monoclonal antibody is an antibody that's produced by a single clone of B cells or a cell line, and consists of identical antibody molecules that can actually be produced in the in-vitro situation

in unlimited quantities.

Next slide.

If you look at the virion on the upper-left part of the slide and you look up the blown-up spike protein — the red molecule on the right upper panel — when you talk about polyclonal antibodies, which result from infection or vaccination, it's a group of antibodies against every aspect of the spike protein, which is the good news. However, the concentration and the affinity of those antibodies can be markedly improved if you get a single cloned antibody — hence the word "monoclonal" — that's against the very specific part of the spike protein that can have a major effect in prevention and treatment.

Next slide.

So, let's look at what we have. We have three anti-SARS-CoV-2 monoclonal antibody products that have currently had Emergency Use Authorization from the FDA. And the EUAs here are for adults and children 12 years of age and older who weigh at least 88 pounds.

There are three of them. There's the Lilly product — the bamlanivimab plus etesevimab. There's the Regeneron project — product, referred to as REGEN-COV. And then there's the GSK and Vir product. Each of these products targets the spike protein of SARS-CoV-2.

Next slide.

So, you can do an indication for these antibodies that are twofold. The first is to treat infection with SARS-CoV-2.

Next slide.

And in this regard, clinical trials have demonstrated that early treatment with anti-SARS-CoV-2 monoclonal antibodies can reduce the risk of COVID-19 hospitalization or death by 70 to 85 percent.

It is important to emphasize that this must be done early in infection and not wait, of course, until a person is sick enough to be hospitalized. That's when you get the best effect.

And again, being an under-utilized intervention, we want people out there, including physicians, as well as potential patients, to realize the advantage of this very effective way of treating early infection.

Next slide.

Now, if you look at the people who should benefit from this, this is a list from the FDA and the NIH treatment guidelines about all of the people who may have significant benefit from this type of therapy if given early in their infection.

I'm not going to go through each and every one of them, but as you can see, there are a number of conditions on this slide that could benefit from the monoclonal antibody treatment after infection.

Next slide.

But there's also the benefit of prevention using monoclonal antibodies.

Next slide.

And we know now that the FDA, just a couple of weeks ago, authorized the Regeneron monoclonal antibody for post-exposure prophylaxis, namely for the prevention of COVID-19 after someone has been exposed to a documented case of SARS-CoV-2.

And even now — and I won't show the data because of lack of time — there are now studies in pre-exposure prophylaxis, as well as other studies in treatment.

So, I'll have on the last slide — next slide — the treatment guidelines panel. We can give you all the information, and it's accessible on the website shown here. And for physicians, patients, and others who want to know how you can get monoclonal antibodies administered, this is the call center and this is the online way to approach it.

So, bottom line is: This is a very effective intervention for COVID-19. It is underutilized, and we recommend strongly that we utilize this to its fullest.

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Please note, as NIH NIAID Case #12276 has been confirmed to exist in the NIAID files by the return phone call I received from "Meg" of the office of Kara Harris, MPH, it would be appropriate under the Freedom of Information Act (FOIA) that with the submission of a written request for a copy of NIAID Case #12276 and some nominal fee to the U.S. Government (usually about \$5.00) any person, media agency, etc. should be able to request a copy of NIAID Case #12276 *in toto*. As I am the claimant for my submissions to the U.S. Copyright Office of the Library of Congress of June, July, November 2020 (and this planned submission), I release any copyright constraints and give permission without any reservations to anyone (including the U.S. Federal Government) to reproduce/copy/publish without any expectation of recompense to me from their reproducing, copying or publishing this report *ad infinitum*. The last time I checked, the FOIA Officer of the NIH NIAID was Ms. Manheim. (In short, all my submissions that are in NIAID Case #12276 are a compendium representative of my duty, as I see it, to the people of the USA for whom I serve as a U.S. Federal Physician & Surgeon.)

Marianne Manheim NIAID FOIA Officer 6705 Rockledge Dr (RK1), 400-C Bethesda, MD. 20892 301-496-9739 Marianne.manheim@nih.hhs.gov

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22.0 9.0 2021-08-22 One year after the first EUA for COVID-19 Convalescent Plasma

Dear Mr. President:

One year ago on the Sunday before the start of the Republican National Convention, President Trump announced an Emergency Use Authorization for COVID-19 convalescent plasma. This was just a small part of the rambling journey our country has taken in the last 18 months in an extremely-confused, disorganized treatment of COVID-19. U.S. Medicine, American Pharma, and such agencies of the Federal Government as the FDA, the NIH, the CDC, and the VA have proclaimed a multitude of mixed messages disingenuously directing the America people regarding COVID-19 by violating their own policies and legal mandates in disregarding or misrepresenting the foundational clinical immunologic and treatment axioms of active immunization, passive immunization, and antivirals in the management of the novel COVID-19 viremia. None of the aforementioned treatment interventions prevents the contraction of COVID-19—it's a cold virus and when exposed, the vast majority of us will contract it.

All the aforementioned agents in the treatment of COVID-19 should be employed in a systematic, organized, synergistic methodology promoting:

- (1) EARLY (<72 hours from diagnosis) treatment and suppression of the *in vivo* COVID-19 viral replication when an individual has contracted COVID-19 with:
 - (a) antiviral agents like Remdesivir and
 - (b) some form of Passive Immunization (COVID-19 Convalescent Plasma or Sera or Monoclonal Antibodies or Antibody Cocktails thus providing exogenous neutralizing antibodies against the COVID-19 virion
- (2) Prior to exposure and contraction of COVID-19, the U.S. is promoting the development of endogenous neutralizing antibodies against the COVID-19 viron with Active Immunization of each individual through vaccination (Pfizer, Mederna, J&J, etc.)
- (3) Regardless of vaccination status, within 72-96 hours of the diagnosis of contraction of COVID-19, every individual should be immediately given that listed in (1) above:

- (a) Passive immunization from an exogenous source such as COVID-19 convalescent plasma or sera or monoclonal antibodies and antibody cocktails
- (b) and an antiviral.
- (4) If a patient does not develop endogenous neutralizing antibodies with vaccination attempts or is immune suppressed by disease or treatments (e.g.: cancer and/or chemotherapy; lymphoproliferative disorders like: leukemias, lymphomas, multiple myeloma, etc.; by immunosuppression due treatment with steroids, monoclonal antibodies, etc. as in rheumatological and chronic inflammatory diseases; etc.), they should be supplemented with some form of Passive Immunization from an exogenous source such as COVID-19 convalescent plasma or sera or monoclonal antibodies and antibody cocktails every 6-8 weeks.

This should be the standard-of-care of every man, woman, and child in the United States of America.

Beginning in the Winter of 2020, the United States direction in the official treatment of COVID-19 has seldom advanced Hippocratic concept of *Primum non Nocere* as primary goal. Using the selfish, narcissistic methodologies of self-promotion by individuals, companies, academia, the U.S. government, etc., we, the American people, have embraced conflicts-of-interest as a standard; routinely impugned individuals in *ad hominum* denunciations; and employed the self-serving mantra of the end-justifies-the-means collectively. How did we do that?:

Putting all our therapeutic "eggs-in-one-basket", we promoted the in-the-future-goal of vaccination (active immunization) as the <u>only</u> viable immunologic treatment methodology and downplayed convalescent plasma (passive immunization) by declaring it *Investigational* instead of a *biosimilar biologic* which would have led to early approval. This disasterous snowball-rolling-down-the-hill was publicly initiated on March 2, 2020 in a White House briefing of the President of the United States by representatives of Departments of the Executive Branch of the Federal Government, representatives from Pharma, and others.

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23.0 10.0 2021-08-12 Triage

Dear Mr. President,

For the last 18 months, U.S. Academia, U.S. Medicine, U.S. Pharma and the U.S. Federal Government have participated and promoted confusion, conflict, and obfuscation in addressing the COVID-19 pandemic. The World yearns for some resolution of this pandemic. As President Kennedy spoke before the American University in 1963:

...What kind of peace do we seek? ... Not the peace of the grave or the security of the slave. I am talking about genuine peace, the kind of peace that makes life on earth worth living, the kind that enables men and nations to grow and to hope and to build a better life for their children—not merely peace for Americans but peace for all men and women—not merely peace in our time but peace for all times...For, in the final analysis, our most basic common link is that we all inhabit this small planet. We all breathe the same air. We all cherish our children's future. And we are all mortal.

As a general surgeon for forty years, the addressing of the pandemic by U.S. medicine and the U.S. government should've been one of triage of a disaster in an organized fashion. The triage categories professed by such institutions as the World Health Organization are that of *Emergency, Priority*, and *non-Urgent*. In the addressing of COVID-19, one could triage today in the following fashion:

- I. **Emergency:** Admit to the hospital <u>ALL</u> who test positive--both asymptomatic and symptomatic. <u>Treat IMMEDIATELY</u> (best within <72 hours of diagnosis) <u>ALL</u> With:
 - a. **Passive Immunization**: COVID-19 Convalescent Plasma or Sera (CCP/S) or Monoclonal antibodies or antibody cocktails (MCA or MCA cocktails)
 - b. An antiviral like Remdesivir (VELKURY), FDA NDA# 214787
 - c. Initiation of **Active Immunization**: The initial dose of a COVID-19 vaccination (Pfizer, Moderna, Johnson & Johnson, etc.)
 - d. Dexamethasone if pneumonitis is present
 - e. Supportive care with oxygen, respirator, ECMO, etc. if indicated
- II. **Priority:** Send home all that test negative for COVID-19 and subsequently track. If they are not yet vaccinated, there should be the initiation of **Active Immunization:** The initiation initial dose of a COVID-19 vaccination (Pfizer, Moderna, Johnson & Johnnson, etc.) and followed-up with the subsequent recommended doses.

If an **individual is immunosuppressed** or does not develop adequate endogenous COVID-19 neutralizing antibody titers to a vaccine regime, the individual should receive some form of exogenous Passive Immunization every 6-8 weeks for the rest of his/her life. Repeat vaccine regimes at later dates should be attempted **BUT** if with subsequent follow-up testing of endogenous COVID-19 neutralizing antibody titers are not adequate, **continued exogenous Passive Immunization every** 6-8 **weeks for the rest of his/her life should be continued.**

If the individuals become symptomatic positive subsequently, admit to hospital: **Treat IMMEDIATELY** (best within <72 hours of diagnosis) **ALL With:**

- a. **Passive Immunization**: COVID-19 Convalescent Plasma or Sera (CCP/S) or Monoclonal antibodies or antibody cocktails (MCA or MCA antibodies)
- b. An antiviral like Remdesivir (VELKURY), FDA NDA# 214787
- c. Continuation of **Active Immunization**: The subsequent dose—the booster--of a COVID-19 vaccination (Pfizer, Moderna, Johnson & Johnson, etc.)
- d. If the patient progresses, initiate subsequent supportive care as per the **Emergency** protocol of I.d & e, etc.

III. Non-urgent:

- a. If individuals test negative and are asymptomatic, send home after the initiation (or continuation) of **Active Immunization:** The initial or subsequent dose of a COVID-19 vaccination (Pfizer, Moderna, Johnson & Johnson, etc.)
- b. If dead, bury as soon as possible.

Since January 2020 when the U.S. government contracted with Regeneron for monoclonal antibody development, U.S. Medicine and the U.S. Federal Government did not clarify nor emphasize to the American public the epidemiologic distinction nor synergy of early administration of *Passive Immunization* (CCP/S or MCA or MCA cocktails) and antivirals (Remdesivir) in treating all COVID-19 positive patients (during early viremia) and *Active Immunization* (COVID-19 vaccines) in, as yet, uninfected individuals. The algorithm above is the appropriate, systematic, strategic addressing of COVID-19 positivity in the EARLY **TREATMENT** of COVID-19 (<72 hours from diagnosis) for every individual that contracts COVID-19 (not rationing or administration to only "high risk" individuals). In the 1970s, small pox was eradicated clinically by the synergistic utilization of massive world-wide Active *Immunization* (vaccination) in individuals naïve to the virus and treatment of those infected and their contacts with *Passive Immunization* (CCP/S or MCA or MCA cocktails). Mr. President, ask Dr. Fauci about this concept regarding treating novel infectious diseases with *Passive Immunization* as COVID-19 is a novel disease to mankind and he was the senior author of *The* New England Journal of Medicine article: "Monoclonal Antibodies for Emerging Infectious Disease—Borrowing from History."

In February 2020, in the *Journal of the American Medical Association*, the Chinese epidemiologic experience was reported without description of treatment. In early March 2020, in a meeting of Pharma with President Trump and key FDA/NIH physicians, the important emphasis of <u>early</u> treatment with *Passive Immunization* with subsequent treatment with *Active Immunization* with vaccines when available was confused—minimizing the clinical utility / necessity of *Passive Immunization*. On March 24, 2020, instead of declaring COVID-19 Convalescent Plasma <u>biosimilar</u> with such agents as Fresh Frozen Plasma (FFP), Rabies vaccine, Tetanus Hyperimmune globulin, RhoGam, Gamma Globulin, and IVIG, the FDA's Center for Biologies Evaluation and Research (CBER) directed by Peter Marks, M.D., Ph.D. declared COVID-19 Convalescent Plasma (CCP) *Investigational*. What-is-more, the FDA issued instructions <u>incorrectly</u> of restrictive/exclusively-<u>LATE</u> eligibility administration criteria for CCP to only hospitalized patients severely ill (albeit, at Death's Door) during the ARDS/severe systemic of the cytokine cascade and the bradykinin storm. The FDA referenced

the February Chinese article once only in the last 17 months on March 24, 2020, as justification for the INCORRECT ELIGIBILITY CRITERA for the late administration of COVID-19 Convalescent Plasma. COVID-19 Convalescent Plasma CCP was **never mentioned** in the paper as a treatment (and yet the Chinese must have used CCP liberally for they offered 90 tons of CCP to Italy in mid-March 2020 after China's internal epidemic was contained and the U.S. epidemic was just starting)¹¹⁶:

2020-03-24 U.S. Food and Drug Administration: Investigational COVID-19 Convalescent Plasma – Emergency INDs, March 24,

2020. https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20" %20FDA.pdf

- Eligible patients for use under expanded access provisions:
 - o Must have laboratory confirmed COVID-19
 - o Must have severe or immediately life-threatening COVID-19, for example:
 - · Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 200 and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - · Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale... 2/

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

- multiple organ dysfunction or failure
- o Must provide informed consent

¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

NO WHERE in the aforementioned reference #1 by Wu and McGoogan upon which officially the U.S. FDA based the Eligibility Criteria for late administration of COVID-19 Convalescent Plasma from March 24, 2020 to September 2, 2020 is "CONVALESCENT", "PLASMA", "ELIGIBILITY" or "CRITERIA" mentioned even once !!!!

What is more, someone in the FDA must have realized the error of misinterpreting / misapplying the Chinese reference because since April 8, 2020 all subsequent FDA documents have failed to reference any justification article for the FDA's Eligibility Criteria of March 24, 2020! On March 26, 2020, the British Medical Journal article reported on the FDA's fallacious criteria and

all the BMJ article's references point to the ex post facto FDA document of April 8, 2020 which makes no mention of the Chinese article nor any justification for the late-administrationeligibility-criteria. The FDA continued this ERRONEOUS administration criteria until quietly removing the criteria from all subsequent documents regarding Remdesivir (August 28, 2020) and COVID-19 Convalescent Plasma (September 2, 2020) without publicly notifying U.S. Medicine, the rest of the Federal Government, and, most of all, the American people. Instead, of advising correction of the administration timing of CCP to all COVID-19 positive patients within <72 hours COVID-19 diagnosis in all NIH Clinical Trials, the NIH encouraged all the trials to continue to completion using this INCORRECT administration late-in-the-disease of individuals that were treated with COVID-19 Convalescent Plasma. (How fantastic would it have been if the FDA and the NIH would have honestly taken ownership of the error in late timing and offered direction to the previously registered NIH Clinical Trials to correct their protocols!) Since the Fall of 2020, the NIH COVID-19 Treatment Guidelines Panel hedged-itbets officially by reprinting "...that convalescent plasma with high antibody titers may be more beneficial than low titer plasma in non-intubated patient, particularly when administered within 72 hours of COVID-19 diagnosis.":

Convalescent Plasma

Last Updated: October 9, 2020

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.¹

Recommendation

 There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic APA data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance.³³ Despite meeting the "may be effective" criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population.⁴⁵ Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing.

The Panel's assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents. $^{3.6.7}$

If <u>High</u>-titer COVID-19 Convalescent Plasma (CCP) is better than Low-titer (CCP), **would not** High-titer COVID-19 CCP be better that No-titer COVID-19?

Over the 2020 Summer, multiple members of The White House COVID-19 Commission continued to advocate for CCP donation. This culminated on July 31, 2020, with members of the Commission bringing President Trump to the American Red Cross National Headquarters adjacent to the Dr. Charles Drew Red Cross Blood and Platelet Donation Center. President Trump praised the concept of COVID-19 Convalescent Plasma that day, but then withheld

announcing it until a nationally-televised White House press conference on the Sunday afternoon of August 23, 2020—the day before the start of the Republican National Convention. With the FDA announcement that evening of an Emergency Use Authorization (EUA), availability of CCP transitioned from the Mayo Clinic/FDA Expanded Access (compassionate use – data not available for formal clinical trials) back to availability only through the formal IND or eIND process of an *Investigational Biologic*. Thus, the availability of CCP became restricted to only Phase 1, 2, 3, or 4 Clinical Trials authorized through the FDA. Even though over 90,000 units of COVID-19 Convalescent Plasma had been administered SAFELY through the Mayo Clinic Expanded Access Program and the Commissioner of the FDA, Steven Hahn, M.D., declared CCP SAFE at the August 23, 2020 White House Press Conference, **NO** Phase I (Safety Study) had been officially "Completed" to fulfill the stipulation of the Right-to-Try Act, PL-115-176. Thus, CCP availability became extremely restricted to de facto mandatory participation in only prospective, randomized, placebo-controlled clinical trials. From August 23, 2020 to September 2, 2020, CCP under the new EUA, the eligibility criteria remained de facto the restricted, timely**incorrect**, administration-late-in-the-course only to hospitalized, COVID-19-positive-severelyill patients. In essence, the timely-incorrect, administration-late eligibility criteria is pervasive throughout the United States to this day. In a parallel fashion, the Veteran Affairs' official "eligibility criteria" posted on the Internet even to this day regarding Remdesivir (VELKURY) approved as non-experimental New Drug (NDA #214787) on October 22, 2020, is the timelyincorrect eligibility criteria even after it was withdrawn by the FDA on August 28, 2020.

As an aside, Mr. President, the NIH has successfully ignored the legally-mandated application of the Right-to-Try Act, PL-155-176, for the last three years even before COVID-19. The stated intent of the Act was for administration of a SAFE *Investigational* (efficacy not proven) new drug or biologic to anyone unable to participate in a clinical trial who had a potentially terminal disease. As was outlined in a CBS Sunday Morning episode about two months ago, the patient suffering from ALS could not access a new durg treatment because he was not eligible for the experimental clinical trial. The NIH has been quite successful at avoiding and alluding the intent of PL-155-176 and applying it by equating **SAFETY** (Phase 1 Clinical Trials) with **EFFICACY** (Phase 2/3 Clinic Trials). Of the official Phase 1 clinical trials of CCP on the NIH ClinicalTrials website, only one was officially "completed" in December 2020 and that was an "Early Phase 1" out of the University of Chicago—I assume that the "Early" in this completed "Early Phase 1" Clinical Trial semantically disqualified this Clinical Trial of the University of Chicago as an officially Completed Phase 1 clinical trial which therefore disqualified the application of the Right-to-Try Act, PL-155-176, for treatment of COVID-19 positive patients within the first 72 hours with Convalescent Plasma. What is more, all the Phase 2 and Phase 3 clinical trials searchable on https://clinicaltrials.gov/ by definition require a PLACEBO control group regarding CCP. All CCP doses administered under **Expanded Access** by definition are "Compassionate Use Only" and thus all the data generated should not be eligible for any Clinical Trials. Prior to April 17, 2021, greater than 722,000 units of CCP have been administered SAFELY-but, almost exclusively at the wrong time, used the now FDAremoved strict eligibility criteria, and a large majority of CCP units were administered under "Expanded Access"!

The NIH is now approving combined phase 1, 2 designations which permits the clinical trial to proceed indefinitely without ever requiring official completion of the phase 1 component. In essence by legal obfuscation, now and into the future, the NIH will never have to allow the application of the Right-to-Try Act, PL-155-176 for any *Investigational New Drug or Biologic*. Thus, while such behavior by the agencies of the U.S. Department of Health and Human Services insensitive to patient's rights and may be morally reprehensible—it does seem to be legal by the NIH's loophole interpretation that allows violation of potentially terminal patients' rights under PL-155-176 applied to any *Investigation New Drug or Biologic*.

On August 12, 2020, a young reporter interning with the St. Louis Post-Dispatch recorded the <u>most saliant issue</u> regarding coercion of patients in PLACEBO-controlled clinical trials—in this case, COVID-19 Convalescent Plasma:

2020-08-12 Kozlov M: Two Washington U. doctors lead national effort to study new COVID-19 treatment. St. Louis Post-Dispatch Aug 12, 2020. https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article_ccec0f56-4493-5a26-8601-45e35d364b2d.html

Since April, the Trump administration has set aside **more than \$300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving highrisk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

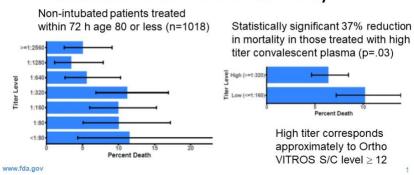
Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

Mr. President, such **implied coercion** for **Placebo**-control-participation in Clinical Trials / Research Medicine is denounced by the Nuremberg Code, the Helsinki Accords, and the Belmont Report. After the Ebola crises, the U.S. Institute of Medicine and the World Health Organization warned the United States that **Expanded Access** (Compassionate Use) should be avoided as any data from such processes could not used in Clinical Trials.

The White House and the FDA on August 23, 2020 tried to justify the EUA issuance on an analysis from the Mayo Clinic Expanded Access "data":

COVID-19 Convalescent Plasma Reduction in Death at 7 Days





Following *The White House* press conference on August 23, 2020, on August 24, 2020, members of the Medical Academia immediately objected in the media to the EUA authorization of CCP; and, importantly, the strict, timely-incorrect eligibility criteria was quietly withdrawn by the FDA two weeks from all FDA documents going forward; **BUT**, it has unfortunately been applied to this day throughout the country even though it is has not been in any FDA documentation since September 2, 2020. On November 24, 2020, in *The New England Journal of Medicine*, one of the continued NIH approved ClinicalTrials where administration was Late-in-the-course-of-the-disease was part of the experimental prospective placebo-randomized prospective trial was published which declared that CCP had not shown efficacy in **hospitalized patients** who suffer from the **COVID-19 induced severe pneumonitis.**

Little notice was taken in the U.S.A., a review article on *Passive Immunization* was published in BioMed Research International regarding the use of convalescent plasma in the treatment of COVID-19:

On March 11th, 2020, the World Health Organization declared COVID-19 infection as a pandemic. Since it is a novel virus, there are basically no proven drugs or therapies; although many laboratories in different countries are working to develop a vaccine, it will take time to make it available. Passive immunization is the therapy born from the intuition of Behring and Kisato in the late 19th century. It was widely used for the treatment of bacterial infections until the discovery of antibiotics, as well as during the viral pandemics of the 20th century and of the beginning of the 21st; it still has clinical applications (e.g., tetanus prevention). This paper summarizes the basic principles of passive immunization, with particular reference to convalescent plasma. The literature concerning its use during past epidemics and the results of the first clinical studies concerning its use during the current pandemic are discussed too. A large section is dedicated to the analysis of the possible, although rare, side effects. Recently, in 2017, the WHO Blood Regulators Network (BRN) published a position paper, recommending convalescent plasma as the firstchoice treatment to be tested in the absence of authorized drugs; however, this strategy has not been followed. In the current epidemic, the principle of passive immunization through convalescent plasma has been applied in several circumstances and particularly in patients with serious complications. The first reported results are encouraging and confirm the effectiveness of plasma therapy and its safety. Also, the FDA has proposed plasma treatment in order to face the increasingly complex situation and manage patients with serious or immediately life-threatening COVID-19 disease. Several studies and clinical programs are still ongoing.

In the latter part of September 2020, Regeneron announced very exciting results of decreased symptomatology in non-hospitalized COVID-19 positive individuals given their monoclonal

cocktail (only early in their disease state)—in deference to the EUA for COVID-19 convalescent plasma in which **hospitalization is mandatory inclusion for administration** (*de facto* late in their disease state) throughout the last year!

This is an incomplete timeline that ends prior to President Trump contracting COVID-19 in October 2020.

What follows is a timeline of my submissions from April 2020 to the present:

- 1. Andrus CH: Time: The crucial *Independent Variable* of the COVID-19 pandemic. U.S. Copyright Office, Library of Congress, Registered unpublished Collective Work, TXu002199029, 6/8/2020.
- Andrus CH: The Mayo Clinic "Safety Update" should be Classified as a Completed Phase I Trial of COVID-19 Convalescent Plasma. U.S. Copyright Office, Library of Congress, Registered unpublished Collective Work, TXu002214049, July 22, 2020.
- 3. Andrus CH: 1 Dear Mr President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. U.S. Copyright Office, Library of Congress, Registered unpublished Collective Work, TXu002232947, 11-18-2020.
- 4. Andrus CH: Letter of December 13, 2020, to the Editors of the NEJM regarding: Simonovich et al: A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. NEJM.org, DIO: 10.1056/NEJMoa2031304, November 24, 2020, 1-11. (Republished by N Engl J Med, February 18, 2021; 384 (7): 619-629). https://www.nejm.org/doi/pdf/10.1056/NEJMoa2031304?articleTools=true The NEJM Editors never responded to my submission which indicated to the reader that COVID-19 convalescent plasma was administered in this randomized trial at the WRONG time, Late-in-thecytokine cascade/bradykinin storm phase of the COVID-19 disease. This article by Simonovich, et al was an INCORRECTLY-timed NIH Clinical Trial conducted using the WRONG administration time and was based on the INCORRECT FDA administration Eligibility Criteria (March 24, 2020 - September 1, 2020) and without age-stratification which was removed from all FDA documentation on September 2, 2020. Consistent with the classical teachings regarding all Passive Immunization agents, RADM Dennis Hinton, R.N, M.S., FDA Chief Scientist, in issuing the EUAs regarding COVID-19 Convalescent Plasma of August 23, 2020 and November 30, 2020 stated: "Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of the disease."

While the NEJM Editors did not directly respond to my *Letter to the Editor*, three weeks later on January 6, 2021, the NEJM published in NEJM.org DIO: 10.1056/NEJMoa2033700: Libster R, *et al*: "Early high-titer plasma therapy to prevent severe Covid-19 in older adults", NEJM.org DIO ClinicalTrials.gov, NCT04479163. (Republished on by the N Engl J Med, February 18, 2021; 384(7): 610-618.) https://www.nejm.org/doi/pdf/10.1056/NEJMoa2033700?listPDF=true This was a landmark article consistent with the foundational teachings of Clinical Immunology regarding **early** administration of *Passive Immunization* in a coherent aged population and RADM Hinton's EUAs for COVID-19 Convalescent Plasma which concluded: Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly infected older adults reduced the progression of Covid-19. (*p* <0.03)

Both of the aforementioned articles were republished on February 18, 2021 and followed by the republication of Louis Katz, M.D. NEJM editorial: Katz LM: "(A Little) Clarity on convalescent plasma for Covid-19." N Engl J Med, February 18, 2021; 384 (7): 666 – 668. (Initially published January 13, 2021).

https://www.nejm.org/doi/full/10.1056/NEJMe2035678

[Please note that Dr. Katz was not fully identified by this paper. Dr. Katz is "...the former Chief Medical Officer at America's Blood Centers in Washington, DC, an ABC past president, former board member and a past chair of its Scientific, Medical and Technical Committee. His transfusion medicine career has been dominated by attention to transfusion transmitted infections. He has served multiple terms as the chair of the AABB Transfusion Transmitted Diseases committee and served on many AABB committee and working groups. Dr. Katz is on the Editorial Board of the journal Transfusion, has served on the FDA Blood Products Advisory Committee as a member, industry representative and chair, and is a current member of the HHS Advisory Committee on Blood and Tissue Safety and Availability." — Winn KI, Katz L, Goel R: Dr. Louis Katz, Acting Chief Medical Director. ImpactLife (formerly Mississippi Valley Regional Blood Center). https://www.bloodcenter.org/about/news/authors/dr-louis-katz-a4/]

PLEASE NOTE THAT ONE SHOULD CAREFULLY READ DR. KATZ'S ARTICLE: Besides confirming that *Passive Immunization* should be given as early as possible in the disease; NO research conclusions can be drawn from Expanded Access (Compassion Use) programs like the Mayo Clinic / FDA Expanded Access program; and as of March 26, 2021, and, as Dr. Katz is the acting Chief Medical Director of ImpactLife (formerly the Mississippi Valley Regional Blood Center), as of March 26, 2021, ImpactLife has stopped accepting donations due to strong inventory stores and decline in COVID-19 hospitalizations:

The supply of convalescent plasma has been tenuous during the marked increase in Covid-19 cases during the fall in the United States, although recent collections have improved. From September 28 through December 27, 2020, distributions of new and stockpiled units of convalescent plasma to hospitals in the United States exceeded collections by 7785 units (Block W: personal communication). If collections are restricted to the high-antibody titers and patient indications described in the article by Libster et al., the supply of convalescent plasma will be stressed. At my center, high-titer collections (as defined by the FDA) account for only 19.5% of seroreactive convalescent plasma donations. Shifting the pool of potential recipients away from those included in the EUA to the many infected outpatients whose risk of hospitalization and eventual need for advanced care cannot be precisely estimated should lead to the extension of convalescent plasma transfusions to prehospital venues (although this is not yet permitted in the EUA).

<u>Uncontrolled compassionate use of convalescent plasma in patients other than those with an early infection that is likely to progress to more severe illness should be discouraged</u>, even though clinicians recognize how difficult it can be to "just stand there" at the bedside of a patient in the ICU. Constraints on therapies for Covid-19 that are effective for limited patient populations are a powerful argument for continued consistent adherence to recommended nonpharmaceutical interventions and the rapid deployment and uptake of effective vaccines.

5. Andrus CH: E-mail communications with the office of the VHA Under Secretary of Health, Richard A. Stone, M.D. regarding the VA's use of the WRONG Eligibility Criteria for the administration of Remdesivir, VELKURY, NDA 214787, December 20, 2020.

In November 2020, the VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives issued: *Remdesivir (VEKLURY)*, *Criteria for Use, November 2020* https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf in which is:

Inclusion Criteria

The following must be fulfilled in order to meet criteria for remdesivir

Hospitalized with **SEVERE** COVID-19 (room air oxygen saturation <94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***

The chronology of the **removal of the severity criteria** is outlined in RADM Hinton's EUA on Remdesivir of October 22, 2020 https://www.fda.gov/media/137564/download, **BUT** the VA has continued the posting without retraction to this day, August 11, 2021.

- 6. Andrus CH: This is a cover letter (e-mail) regarding my letter to the Editors of *The New England Journal of Medicine* regarding: Simonovich VA, Burgos Pratx LD, Sciboona P, et. al.: A Randomized Trial of Convalescent Plasma in Covid-19 severe pneumonia, November 24, 2020. (email attachment item: "41 Letter to editor 12_13-2020 Not yet sent 12-20-2020.docx"). Sent December 24, 2020 to the Editors of *The New England Journal of Medicine*.
- 7. Andrus CH: A letter of January 27, 2021, to Dr. Deborah Birx, M.D., former Chair of the Presidential COVID-19 White House Commission after her interview by Margaret Brennan on Face the Nation of January 24, 2021: https://www.cbsnews.com/news/full-transcript-dr-deborah-birx-on-face-the-nation-january-24-2021.
- 8. Andrus CH: Letter to Dr. Birx, former Chair of the Presidential Commission on COVID-19 in response to her interview by Margaret Brennan which aired on CBS Face the Nation on January 24, 2021.

Andrus CH

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24.0 11.0 2021-07-25 Please stop the NIH and the FDA from ignoring Public Laws, their Own Policies, and Statutory Responsibilities

Dear Mr. President,

While driving in the car yesterday, July 24, 2021 at ~4:00 PM CDT, I heard on KMOX (the "Radio Voice" of the St. Louis Cardinal's Radio Station), I heard the commentator ask of the physician expert being interviewed what are the options available to us now going forward in COVID-19 pandemic. The physician expert emphatically replied: Increased vaccinations and masks. He then elaborated that at present while medical personnel are tired, we have enough ventilators, etc. Mr. President, what happened to treating the virus when an individual contracts it -- EARLY (within 72 hours) in the initial viremic stage of the disease to every person?

As I have been communicating (and documenting for history in the U.S. Copyright Office of the Library of Congress since June of last year), this cover letter hopefully will present to you the medical strategy that we should now chart in our overall addressing of the ongoing COVID-19 epidemic in the United States. A COVID-19-pathophysiologic-based treatment algorithm that is all-encompassing with regards to **PREVENTION** and **Treatment** <u>must</u> be implemented. While we have as a nation focused on the success of vaccination (Active Immunization) in stimulating the immune naïve individual to develop COVID-19 neutralizing antibodies, we (U.S. Medicine) for the last 16 months have *de facto* withheld from the American people and thus failed the general public in the provision of an organized treatment protocol in the **EARLY** days of each individual's contraction of COVID-19—that is, during the initial <u>viremic phase</u> of the disease (within < 72 hours of diagnosis). During that period, we have *failed to treat immediately after diagnosis* every man, woman, and child with some form of Passive Immunization agent (COVID-19 convalescent plasma or sera or monoclonal antibody cocktails) and the antiviral drug VELKURY (remdesivir), NDA #214787.—which we should have done.

U.S clinical, research, and organized Medicine; the agencies of the U.S. Department of Health and Human Services, and U.S. Businesses protected their vested interests at the cost of American lives (e.g.: by unethically coercing individual participation in placebo-controlled Clinical Trials—THE VAST MAJORITY performed at the WRONG TIME in the pathophysiologic course of the disease--administration of COVID-19 convalescent plasma only at-the-end-of-life disease phase rather than EARLY in the viremic phase (<72 hours from diagnosis); employing legal obfuscation to dismiss the individual's rights that should have been protected under EMTALA, PL-99-272 and the Right to Try Law PL-115-176; AND amassing fortunes by avoiding application of these public laws at the expense of U.S. citizens, etc.)

Mr. President, why was **NOT EVERY AMERICAN WHO CONTRACTED COVID- 19 OFFERED** *Passive Immunization and the antiviral agent Remdesivir EARLY* in the course of their diseases (<72 hours from time of diagnosis) as was afforded former President Trump, former HUD Secretary Carson,

former Governor Christie, and former N.Y. Mayor Guiliani early in the course of their COVID-19 diseases in October of 2020?

Mr. President, U.S. Medicine, the U.S. Government, and all the U.S. Businesses that made money at the expense of people's lives and well-being should **APOLOGIZE** to the American people. Going forward:

- 1. Any individual who contracts and is diagnosed with COVID-19 should be offered immediate treatment (within 72 hours of COVID-19 diagnosis) with some form of Passive Immunization and some antiviral drug. This should include all unvaccinated individuals, vaccinated that did not mount an antibody response to the vaccination, and all immunocompromised individuals. (All individuals that have minimal levels of Neutralizing Antibody titers after vaccination should be placed on an every 6 8 week prophylactic administration regimen of Passive Immunization (e.g.: monoclonal antibodies) for the rest of their lives or until they are assayed to demonstrate antibody titers.) This should be the Medical standard-of-care not only in the U.S.A. but should be encouraged throughout the world. [When smallpox was finally eradicated from the World in the 1970s, it was not just Active Immunization alone (cowpox vaccination which humanity had been employing for 200 years) that help accomplish this feat but also Passive Immunization (small pox convalescent plasma) that was given in the early treatment of individual active smallpox victims and prophylactically to their unvaccinated contacts.]
- 2. BARDA should be disbanded for there is TOO much possibility of inherent financial conflict-of-interest that has been driving medical research!
- 3. As the Head of the Executive Branch of the United States Government, could you, Mr. President, please STOP the *de facto* practice of electronic overwriting of all agencies' policies, directive, handbooks, etc. by issuing an Executive Order to that effect. Such an Executive Order could reinstate the previous universal U.S. Executive Branch of the Federal Government practice of rescinding a document with certification that the previous rescinded document could be found! Expunging information contained in an official U.S. Executive Branch of the Federal Government URL website so the information is not legally discoverable or deleting or destroying information of an official U.S. Executive Branch URL website should be proscribed and prohibited as this is UNETHICAL (and even now may be illegal but ignored).
- 4. At present, the FDA and the NIH should NOT avoid or violate Federal Law (e.g., PL-99-272 and PL-115-176). A national debate should once again be initiated about the unethical nature of placebo-controlled Clinical Trials where an individual's death is possible as such Clinical Trials violate the intent of the Nuremburg code, the Helsinki Accords, and the Belmont Report. (Not offering treatment to all COVID-19-infected individuals early-in-the-course-of-their-disease with Passive Immunization and an

antiviral agent like remdesivir is unconscionable and equivalent to the withholding of penicillin to the African-American sharecroppers in the Tuskegee Syphilis Clinical Trial when penicillin became available.) There are enough Americans who have now survived COVID-19 without early treatment with Passive Immunization and/or remdesivir that case-matched controlled Clinical Trials should be utilized. In the 1980s, antibiotic placebo Clinical Trials were discontinued as being unethical after such articles as that of Ronald Busuttil, M.D., F.A.C.S. in which the placebo group (no antibiotic) in non-ruptured appendicitis had a 13% wound infection rate versus the antibiotic-treated non-ruptured appendicitis group <1%.

All physicians since Hippocrates have sworn *Primum non Nocere* -- withholding Passive Immunization and the antiviral drug remdesivir is a violation of that pledge.

Mr. President, I have tried in my daily life to do that which is consistent with A.M.D.G. (Ad Majorem Dei Gloria—To the Greater Glory of God—St. Ignatius of Loyola); Primum non Nocere (First, do no harm—Hippocrates); ...to care for him who shall have borne the battle and his widow and his orphan... (Abraham Lincoln); and I promise to deal with each patient as I would wish to be dealt with if I were in the patient's position... (fellowship pledge of the American College of Surgeons). As physicians, it is our obligation to advocate and care for each individual patient. As Francis W. Peabody, M.D. stated almost 100 years ago:

...for the secret of the care of the patient is in caring for the patient...

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.

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25.0 12.0 2021-07-22 Early Timeline from 2/2020 to 8/12/2020: We missed the boat completely as a country with regards to antibody treatment in the initial phase of the viremia of COVID

[See Number 42 on the last page of this submission which epitomizes the FDA's/NIH's insistence in PLACEBO-controlled trials during the COVID-19 Pandemic and the Ethical Debate that should be up-front regarding "Expanded Access", "Placebo control", etc.!]

Dear Mr. President:

For the last sixteen months, our (U.S. Medicine's) collective relative silence regarding Passive Immunization in the early treatment of COVID-19 in all newly-infected individuals (<72 from symptoms or diagnosis during the initial viremic phase) has completely missed the boat. For the last 17 months, the NIH, the FDA, and U.S. Medicine have all found ways to confuse, confound, obfuscate, and inhibit the appropriate, early clinical application of *Passive* Immunization during the viremic phase of COVID-19, which is complimentary to Active Immunization (vaccination). Passive Immunization has been used successfully in viral epidemics multiple times over the last century including used in concert with vaccination in the ultimate eradication of Small Pox. Passive Immunization (giving previously-formed neutralizing antibodies from convalescent patients to newly-infected individuals and prophylactically in high-risk-of-contact individuals with convalescent plasma, donor convalescent serum, or monoclonal antibodies/antibody cocktails manufactured from donor convalescent plasma cells) has been the sine quin non in our treatment of novel viruses over the last century. In 2018, the strategy of early use of Passive Immunization with the administration of monoclonal antibodies to all infected and exposed, non-vaccinated individuals in the treatment of novel viruses was eloquently outlined by Hilary D. Marston, M.D., M.P.H. in the New England Journal of Medicine (NEJM) review article, entitled: Monoclonal antibodies for emerging infectious diseases – Borrowing from history. (Dr. Fauci was the senior author of the article.)

From March 2020 to the present, United States Medicine in concert with the FDA and NIH have minimized the importance and have misled the American people regarding the necessity of administration of Passive Immunization in the early treatment (<72 hours) of COVID-19 during the initial viremic phase of COVID-19 with such passive immunization agents as convalescent plasma, convalescent serum, and monoclonal antibodies, etc. for all. In March 2020, instead of signifying convalescent plasma (biosimilar to the rabies vaccine of Louis Pasteur, Hypertet, RhoGam, gamma-globulin, IVIG, smallpox convalescent plasma, etc.) as a biosimilar biologic, the FDA deemed it: Investigational--leading clinical and research U.S. Medicine and all of the United States of America down the proverbial rabbit-hole—and, at present, we are stuck there! Due to a misinterpretation of the Chinese epidemiology paper of February 2020 published in the Journal of the American Medical Association (JAMA), instead of encouraging the early admission to the hospital of all COVID-19 infected patients as the Chinese article stated, COVID-19-infected individuals in the U.S.A. diagnosed early-in-the-course of the disease were advised to stay at home by such authoritative figures as the U.S. Surgeon General. Such delay in hospitalization facilitated with each passing day infected individuals without Passive Immunization administration moving rapidly into the bilateral pneumonic/ARDS phase of COVID-19 resultant from the cytokine cascade and bradykinin accumulation. Even with

vaccination today, the reported 10% of individuals that don't mount an immune response to the vaccines and those who are immune suppressed—e.g.: transplant patients, patients under treatment of other diseases with monoclonal antibodies and cocktails, etc.—would undoubtedly benefit from some form of *Passive Immunization* administered early (<72 hours) in **every** newly diagnosed COVID-19-infected individual.

My correspondence with the FDA, the NIH, and *The White House* over the last 16 months was akin to a *Cat and Mouse* game where in many instances, I would submit research-validated documentation regarding agents of Passive Immunization and the antiviral drug Remdesivir and, within days, a Federal Agency would respond in public without any acknowledgement of the issue that they were responding to or ignore the information provided that was absolute contradiction to another agency's advisement. The abbreviated time-line is as follows:

- 1. In early February 2020, Regeneron was awarded a federal grant through BARDA to develop monoclonal antibodies to be used against COVID-19. Regeneron is documented in the literature to have been recompensed at least \$3 billion over the course of the last 20 months regarding their COVID-19 monoclonal antibody cocktails and sera.
- 2. On February 24, 2020, an article from China was published in in JAMA entitled: Characteristics of an important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. It never mentioned treatment with COVID-19 Convalescent Plasma yet this article would be used for the FDA in the justification of administration of COVID-19 Convalescent Plasma AT THE WRONG TIME! In the misinterpretation of this article, it became the only justification referenced in the March 24, 2020 initial announcement of Investigational COVID-19 Convalescent Plasma by the U.S. Food & Drug Administration (FDA) to strictly direct the administration of COVID-19 convalescent plasma late-in-the-course of the disease to ONLY severely-ill hospitalized patients WHICH IS THE WRONG TIME. (This is March 24, 2020 FDA announcement is the only place where "1" is printed with the late-in-the-course criteria!—and reportedly, some 722,000 doses of COVID-19 convalescent plasma have been given over the course of the last 16 months mainly late-in-the-course of the disease which is at the WRONG time) While the March 24, 2020 FDA announcement was documented by the British Medical Journal (BMJ), NBC News, and National Public Radio (NPR) at the time, the FDA would expunge this reference "1" from all subsequent delineations of this incorrect administration criteria and direct the BMJ, NBC News, and NPR references listed to the ex post facto FDA announcement of April 8, 2020 which was devoid of the justification reference. What follows is the original FDA announcement of March 24, 2020:

· Eligible patients for use under expanded access provisions:

- Must have laboratory confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale...

2/3

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

- multiple organ dysfunction or failure
- · Must provide informed consent

¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

- 3. On March 2, 2020, Dr. Leonard Schleifer, CEO of Regeneron Pharmaceuticals, (in the presence of Dr. Fauci and HHS Secretary Azar) publicly instructed President Trump as to the difference between vaccination (Active Immunization) and monoclonal antibodies (Passive Immunization). Both monoclonal antibodies and convalescent plasma/sera are agents of Passive Immunization. The FDA's designation of COVID-19 Convalescent Plasma as *Investigational* with the strict severity-of-COVID-19 illness criteria instead of *Biosimilar* would be a definite advantage for Regeneron's development, testing, and subsequent implementation for <u>only</u> asymptomatic or mildly, non-hospitalized COVID-19 positive patients in deference to COVID-19 Convalescent Plasma.
- 4. On March 13, 2020, Dr. Casadevall (Johns Hopkins School of Medicine) and Dr. Pirofski (Albert Einstein College of Medicine)—presently, the World authorities on *Passive*

Immunization--publish in the Journal of Clinical Investigation: The convalescent sera option for containing COVID-19.

A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms.

- 5. On March 13, 2020, President Trump proclaimed a national emergency regarding the novel coronavirus outbreak.
 - a. Section 1. Emergency Authority. The Secretary of HHS may exercise the authority under section 1135 of the SSA to temporarily waive or modify certain requirements of the Medicare, Medicaid, and State Children's Health Insurance programs and of the Health Insurance Portability and Accountability Act Privacy Rule throughout the duration of the public health emergency declared in response to the COVID-19 outbreak.
- 6. On March 13, 2020, Secretary Azar waived the requirements under section 1135 of the Social Security act.

De facto, I allege that the interpretation of this document became the justification of abridgement of individual American rights to Passive Immunization and the antiviral drug Remdesivir, guaranteed under EMTALA (the Emergency Medical Treatment and Labor Act of COBRA Consolidated Ominbus Budget Act of 1986, PL99-272), and the Right to Try Act of 2018, PL-115-176.

- 7. On March 14, 2020, it was documented that the Chinese were sending a medical team to Italy to train the Italians on the use of COVID-19 Convalescent Plasma. (At the time, the Johns Hopkins University website has stated that China offered 90 tons of COVID-19 Convalescent Plasma to Italy-- ~500,000 doses.)
- 8. On March 17, 2020, the Declaration under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 of Secretary Azar is published in the Federal Register retroactive to March 1, 2020 which *de facto* suspended sanctions regarding some of the protections of patient's rights under EMTALA.
- On March 18, 2020, in the Proceedings of the National Academy of Sciences of the United States of America, the Chinese publish: Effectiveness of convalescent plasma therapy in severe COVID-19 patients. https://www.pnas.org/content/pnas/117/17/9490.full.pdf
- 10. On March 19, 2020, U.S. Surgeon Adams publishes the Public Service Announcement: "If You Are Sick"—which is no longer available unless logging in under facebaook: https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/

As the Nation's doctor, I often get asked: What should I do if I think I might have coronavirus? Well, it is important to know the symptoms—they include: fever, cough, and shortness of breath. If you are having these symptoms or worry you might have coronavirus, please call your healthcare provider. We don't want you to go into the ER or the doctor's office without talking to them first because you might spread coronavirus to someone else. They will help you think through and learn how to react including figuring out where to go to get tested if necessary.

11. On March 19, 2020, Brian W. Simpson, Editor-in-Chief, Global Health NOW, Johns Hopkins Bloomberg School of Public Health https://www.globalhealthnow.org/2020-03/covid-19s-stop-gap-solution-until-vaccines-and-antivirals-are-ready

wrote:

How can plasma be useful against the novel coronavirus?

When you recover from many viral diseases, you have in your blood what are called neutralizing antibodies. These are antibodies that kill the virus. Once you recover, the plasma be taken from donors. It's very safe. It's the same thing as using a blood donation except they don't take the red blood cells, they take the liquid. They take the plasma. It is itself a drug...it can be used for prevention of infection for people who are being exposed or it could be used for therapy for those who are sick.

It's not a vaccine. Think about it as the administration of a protein, it's a liquid that is given to people that gives them immunity.

Right. Because the vaccine would provoke the recipient's antibodies. You'll have the antibodies, but they won't be your antibodies—though it'll do the same thing.

Right.

And if somebody is already sick, can the plasma help them? Yes, it can be used for prevention or a treatment.

This strategy is already being used in China?

Yes, in fact, the Chinese sent 90 tons of plasma to Italy.

- 12. On March 24, 2020, Dr. Yancopoulos of Regeneron Pharmaceuticals is quoted in speaking in South Korea: Coronavirus Update: South Korea's Celltrion progresses antibody, Yancopoulos: 'The World is Counting on Us' Antibody Therapies could ease huge burden on emergency care.
- 13. On March 24, 2020, the FDA issues it's first authorization of COVID-19 Convalescent Plasma as an *Investigational* biologic—NOT a *biosimilar* biologic which initiates all that is to follow over the last 16 months. This the <u>only FDA official publication</u> of the late-in-the-disease administration criteria of COVID-19 Convalescent Plasma referencing INCORRECTLY the February 24, 2020, Chinese article in JAMA dictating the late-administration-at-the-end-of-the-disease directive that would be continued in all FDA and NIH documents from March 24, 2020 until September 2, 2020. This can be located <u>only</u> by using the Internet Archive out of San Francisco (the Wayback Machine) https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf

- Eligible patients for use under expanded access provisions:
 - o Must have laboratory confirmed COVID-19
 - Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale... 2/3

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Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

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14. On March 26, 2020, the British Medicine Journal documented the FDA announcement of Investigational COVID-19 Convalescent Plasma and has three confirmatory references of the initial March 24, 2020 FDA announcement document. All three references in the British Medical Journal point subsequently to the URL of April 8, 2020 that the FDA substituted in which the ex-post facto documentation does not contain "1" and thus does not list the Chinese reference Wu Z, McGoogan JM. THIS WAS THE ERROR THAT CONTINUED THE INAPPROPRIATE LATE-IN-THE-DISEASE ADMINISTRATION CRITERIA FOR COVID-19 CONVALESCENT PLASMA (March 24, 2020 to September 2, 2020) and VELKURY (REMDESIVIR from April 2020 to August 28, 2020).

15. On April 4, 2020, the website (First date digitally preserved by the Internet Archive (Wayback Machine).

https://web.archive.org/web/20200404010134/https://www.uscovidplasma.org/) of the FDA/Mayo Clinic Expand Access (compassionate use—prohibited by FDA and NIH guidelines to be used for official Phase I, II, or III Clinical Trials) for COVID-19 Convalescent Plasma coordinated by Michael Joyner M.D., the Principal Investigator, was initiated in which >94,000 hospitalized, severely-ill patients late-in-the-disease between 4/4/2020 to 8/23/2020 were administered COVID-19 Convalescent Plasma SAFELY at the WRONG TIME in the use of *Passive Immunization* due to the WRONG ADMINISTRATION CRITERIA directed by the FDA from March 24, 2020 to September 2, 2020. This is directly from the Mayo clinic website of April 4, 2020:

The protocol requires the patient or family member to consent to receiving plasma from someone who has recovered from COVID-19. Their plasma has substances that could improve chances of recovery. Only hospitalized patients referred by their health care provider will participate in this protocol.

Hospitalized patients are eligible to receive convalescent plasma if:

- They are 18+ years of age
- They have laboratory-confirmed diagnosis of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19
- They are admitted to an acute care facility for the treatment of COVID-19 complications
- They have severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
- There is informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:

- Shortness of breath (dyspnea)
- Respiratory frequency ≥ 30/min
- Blood oxygen saturation ≤ 93%
- Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- Lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:

- Respiratory failure
- Septic shock
- Multiple organ dysfunction or failure

Even though the World Health Organization and the Institute of Medicine warned the U.S.A. after the Ebola crisis to AVOID implementing Expand Access (Compassionate Use) regarding Convalescent Plasma—that is exactly what the FDA did! Even though 94,000 patients through the Mayo Clinic/FDA Expanded Access program were given COVID-19 Convalescent Plasma safely, the results cannot be used to confirm the completion of a "Phase I (Safety) Clinical Trial" as no compassionate use data is allowed in Phase I, II, or III Clinical Trials. Thus, the FDA and the NIH circumvented the intent of the Right to Try Act of 2018, PL-115-176, from April 4, 2020 through September 1, 2020.

- Mr. President, should not Attorney General Garland be requested to review the FDA's and the NIH's circumventing of the stated intent of PL-115-176?
- 16. On April 8, 2020, the U.S. Food & Drug Administration established the website that continues today: *Recommendations for Investigational COVID-19 Convalescent Plasma* which from April 8, 2020 to September 1, 2020 contained the mandated late-in-the-disease administration only in severe or immediately life-threatening COVID-19. https://web.archive.org/web/20200413010215/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment ProtocolExternal Link Disclaimer. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300.
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.
- 17. On April 13, 2020, the FDA issued the first of many: U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma Guidance for Industry. https://web.archive.org/web/20200414181056/https://www.fda.gov/media/136798/download The practice of Overwriting "renewed" Federal policies--instead of documenting a "RESCINDING" of the immediate previous document and it's previously published date—has been EXTENSIVELY employed by the FDA and NIH of the U.S. Department of Health and Human Services throughout the Pandemic which de facto covering up has become a methodology of covering-up of previous directives and misadventures. The ongoing website that has been OVERWRITTEN multiple times in this case is: https://www.fda.gov/media/136798/download

Using the Wayback Machine of the Internet Archive (out of San Francisco-https://archive.org/web/) and knowing the base URL (sometimes the base URL is changed or destroyed), one can usually locate all previously overwritten documents that

have been in that specific URL.—**BUT** isn't **Overwriting instead of documenting the Rescinded policy, handbook, etc.** a surreptitious, non-transparent process.

Mr. President, should there be a Presidential Executive Order regarding the Executive Branch of the Federal Government that discontinues the overwriting electronically of federal documents and reinstates the previous process of documenting "rescinding and dating" of the previous existing document so a paper-trail is preserved?

18. On April 13, 2020, Gibson Dunn's FDA round-up: Overview of emergency actions to expedite the availability of medical products to combat COVID-19.
https://www.gibsondunn.com/wp-content/uploads/2020/04/fda-round-up-overview-of-emergency-actions-to-expedite-the-availability-of-medical-products-to-combat-covid-19.pdf On pages 14 – 15:

There are no FDA-approved drugs or vaccines to treat or cure COVID-19, but at the end of March, FDA launched the Coronavirus Treatment Acceleration Program (CTAP), a special emergency program to expedite the development of COVID-19 therapies. The CTAP program is using "every tool at the agency's disposal" to provide "ultra-rapid, interactive input." [41] FDA has turned around reviews on COVID-19 development plans within 24 hours and completed reviews of single-patient expanded-access requests within three hours. FDA has redeployed medical and regulatory staff to serve on review teams dedicated to COVID-19 therapies. FDA also has streamlined the process for developers and physicians to contact FDA with inquiries and to submit requests for the emergency use of investigational products. FDA is prioritizing these requests based on factors such as the product's scientific merits and the stage of development. In addition to clinical studies, FDA is looking at real-world data sources to inform its evaluation of potential therapies, and FDA is leveraging scientific information being generated in China, Italy, Japan, and South Korea.

According to FDA, there are currently 10 therapeutic agents in active trials and 15 therapeutic agents in planning stages, and the Agency will publish updates as these therapies progress through the development process. Examples of potential therapies and vaccines include the following:

) Remdesivir. Remdesivir is an investigational broad-spectrum antiviral treatment, which was previously tested to treat diseases caused by other coronaviruses, such as Ebola. FDA has been working with Gilead Sciences, Inc. to expedite the clinical studies of remdesivir in adults diagnosed with COVID-19 and to permit the emergency use of the drug through an expanded access program. In March, Gilead began enrolling patients in two Phase 3, randomized, open-label, multicenter clinical studies. One of the studies will evaluate the safety and efficacy of two dosing durations in addition to the standard of care for patients with severe COVID-19. The other study will evaluate the same dosing regimens in addition to the standard of care for patients with moderate COVID-19. Other ongoing studies of remdesivir include the NIAID Phase 2 adaptive, randomized, double-blind, placebo-controlled trial and studies in China and France.

) Convalescent Plasma. Convalescent plasma, collected from individuals who have recovered from COVID-19, contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19). Use of convalescent plasma as a therapeutic agent has been studied in prior outbreaks of respiratory infections, such as the H1N1 influenza pandemic. Earlier this month, FDA entered a

collaboration with BARDA, the American Red Cross, and the Mayo Clinic to simplify the process for health care providers to collect, distribute, and use convalescent plasma in patients. As a result of this collaboration, FDA estimates that thousands of units of plasma will be available to patients within the coming weeks. FDA also is working with NIAID to coordinate a study of hyperimmune globulin, which is a biological product manufactured from convalescent plasma.

On April 8, 2020, FDA issued guidance on the administration and study of investigational convalescent plasma during the public health emergency.[42] Prior to this guidance, FDA had approved emergency INDs for the use of convalescent plasma in very ill COVID-19 patients. The guidance provides recommendations regarding the regulatory pathways for using investigational COVID-19 convalescent plasma, patient eligibility, the collection of COVID-19 convalescent plasma from donors, labeling, and record-keeping. In addition to the traditional IND pathway (21 C.F.R. Part 312), convalescent plasma may be permitted for investigational use through an expanded access IND for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 C.F.R. § 312.305) or through single patient emergency INDs following the request by a licensed physician (21 C.F.R. § 312.310). The convalescent plasma should be obtained from an FDA-registered blood establishment that follows the donor eligibility criteria and donor qualifications. Donors should have complete resolution of symptoms at least 28 days prior to donation or complete resolution of symptoms at least 14 days prior to donation and negative COVID-19 test results. FDA is relaxing requirements relating to the registration, licensure, and procedures of blood establishments that collect and distribute the convalescent plasma for investigational use.

On April 16, 2020, the explanation of how China stop the epidemic was printed in: Wired, News Archives UK: The blood of coronavirus survivors could help cope with the pandemic. https://www.wired.co.uk/article/coronavirus-blood-plasma-trials

The following was copied verbatim for documentation at the time of how China stopped there COVID-19 epidemic:

In late January, hospitals across China began using convalescent plasma as a treatment for Covid-19, and in recent weeks other countries have followed suit after the publication of initial results from Wuhan and Shanghai. While these trials involved just a small handful of patients, they received global attention as they appeared to demonstrate that convalescent plasma could aid recovery in even the most critically ill patients.

"This is amazing because the vast majority of people thought that convalescent plasma could only be effective if administered early in the disease course," says Daniele Focosi, a transfusion specialist at Pisa University Hospital in Italy. "But the Chinese case series has proved clinical benefit even at a late stage which is very intriguing because it could be a life saving treatment."

As of April 6, it was reported that 19 clinical trials of convalescent plasma are already taking place in China, the US, Italy, Iran, Mexico, and Colombia, with more planned. This week Italy is launching a nationwide initiative co-ordinated by Focosi's team at Pisa University Hospital which will use convalescent plasma in hospitals across five more of Italy's 20 regions, complementing an existing trial taking place in Lombardy, the epicentre of the Italian outbreak.

In the UK, the NHS is currently seeking donors for two trials of its own which will compare convalescent plasma against other experimental medications such as antiviral drugs. "One of these trials is to treat patients with Covid-19 pneumonia who have not reached the stage of ventilation to try to stop that happening," says David Tappin, of the University of Glasgow School

of Medicine, who is looking to obtain approval to run his own trial looking at whether convalescent plasma can help protect NHS workers. "The other is to treat severely ill patients already ventilated to try to reduce time on ventilators and to reduce death."

But finding suitable donors is not as straightforward as it might seem. While there are more than 400,000 people around the world who have recovered from Covid-19, the rapid mutation rate of the virus as it has passed between countries means that donors have to be sourced locally. As the pandemic in Italy worsened last month, China reportedly offered to ship 90 tons of convalescent plasma to Italian hospitals for emergency use, but tests soon showed that it could not be used.

"We have evidence that the envelope protein called the spike protein is mutating," says Focosi, who is one of the co-investigators leading the new multi-centre trial in Italy. "So convalescent plasma collected in China may not be protective for Covid-19 patients in Europe and the US. You need antibodies derived from infection to the same strain which is circulating in your area."

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20. On April 17, 2020, the following was published using the previous experience of using convalescent plasma in SARS-1:

Langi DM, Jr., DeSantis GC, Bordin JO: Covid-19 convalescent plasma transfusion. Hematol Transfus Cell ther. 2020 Apr-Jun; 42(2): 113-115.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164882/pdf/main.pdf

... Therefore, all therapeutic options for the potentially lethal COVID-19 infection must be discussed ethically and scientifically. Historically, convalescent plasma (CP), a passive immunotherapy, has been used as a possible therapeutic option when no proven specific vaccine or drug is available for emerging infections.1,2 The administration of convalescent plasma or immunoglobulins has been shown to shorten the hospital stay and reduce the mortality rate in patients with SARS who did not respond to methylprednisolone in uncontrolled non-randomized clinical trials.3,4 Cheng et al. investigated 1775 SARS patients and found that 80 patients transfused with SARS convalescent plasma had a lower mortality rate, compared to non-transfused patients (12.5% vs. 17%).⁴

Conclusions:

Analogous to the SARS, the COVID-19 infection progresses with an intense inflammatory response that eventually causes serious lung damage, increasing the mortality risk. In the absence of a definitive curative management, many treatment algorithms have been explored in the treatment of the COVID19. Among possible interventions, the use of plasma collected from recovered patients shows an initial promise, however published results of rigorous clinical trials are needed before we may draw definitive effectiveness conclusions on this passive antibody therapy.

The administration of the COVID-19 convalescent plasma must, however, fulfill some requirements related to availability of COVID-19 recovered donors: well-designed study protocols to guarantee the efficacy analysis of such an intervention; governmental and institutional compliance, and; laboratory support to perform serological and molecular assays, including the measurement of viral neutralization and immune response. ¹¹ In addition, the connection between hospitals, blood centers and the plasma industry must follow flawless strategies, as plasma units may be frozen before distribution or be manufactured as concentrated COVID-19 immunoglobulin.

21. On April 29, 2020, in the oval office, Dr. Fauci announced that Remdesivir in a prospective, placebo-controlled study was demonstrated to decrease hospital course from 15 days in the placebo control versus 11 days in the Remdesivir group, p value = 0.001. [Gittleson B: Trump, Fauci tout 'good news' from remdesivir drug trial in treating COVID-19. ABCNews 29 Apr 2020. https://abcnews.go.com/Politics/trump-fauci-toutgood-news-remdesivir-drug-trial/story?id=70407208] What this meant was that the process should have been initiated for the immediate administration of Remdesivir to every person in the U.S.A. when they tested positive regardless of symptomatology. Instead, the same criteria only in COVID-19-severely-ill patients for the administration of COVID-19 Convalescent Plasma was applied regarding the administration of Remdesivir. In late August 2020, with the announcement of the EUA by President Trump regarding COVID-19 convalescent plasma on August 23, 2020, I sent ~537 notifications by U.S. Postal Service to every U.S. Senate and U.S. House of Representative office pointing out the safety and utility of COVID-19 convalescent. Within days of those notifications, the FDA removed the late-in-the-disease, severely-illpatient-only criteria regarding both Remdesivir (August 28, 2020) and COVID-19 convalescent plasma (September 2, 2020).

Remdesivir was given a prescription NDA (New Drug Approval) #214787 on October 22, 2020 so any licensed physician in the U.S.A. could prescribe the drug which is specifically designated as a treatment of COVID-19:

This new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

As you will see in the attached correspondence, the U.S. Department of Veteran Affairs continued the severely-ill patient criteria as the Inclusion Criteria in the use of Remdesivir in the VACO policy directive [Remdesivir (VEKLURY) CFU] in November 2020 and as Acting Under Secretary knew of this, the policy has yet to be rescinded even though it is in contradiction to FDA NDA #214787.

https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf (3 months after the severely-ill patient criteria was *de facto* surreptitiously dropped by the FDA in all its documentation and 2 weeks after VEKLURY (remdesivir) became an official FDA-approved prescription drug in the treatment of COVID, NDA #214787. (Mr. President, should you not ask Attorney General Garland if this VA policy is in violation of federal law?).

On CBS's Face the Nation one month ago (June 6, 2021), former FDA Commissioner Scott Gottlieb, M.D. (https://www.cbsnews.com/news/transcript-scott-gottlieb-face-the-nation-06-20-2021/) stated:

That's right, and I think that this could be a real game changer. This is a virus that we should be able to drug. The machinery that this virus uses to replicate are things that we've drugged before. It's not a- it's not a very wily virus. It's not a virus that should evade our drug development tools. So I think that we will have a drug that inhibits viral replication. Pfizer, the company I'm on the board of, is working on one. Merck is working on another one in advanced development. There's a number of other companies also engaged in this pursuit. I think we will get a drug that inhibits viral replication that could be taken on an outpatient basis and is basically like a Tamiflu for coronavirus that you could take when you first have symptoms, when you first have a diagnosis to prevent the progression to disease

Mr. President: We (the FDA, the NIH, the VA, and all of U.S. Medicine) have had an antiviral drug that inhibits viral replication for the last 15 months. When will we give to every person within 72 hours of turning(testing) positive for COVID-19 VELKURY (remdesivir)?

22. On May 1, 2020, the FDA Chief Scientist, RADM Hinton issued the first EUA regarding Remdesivir.

https://web.archive.org/web/20200501204823/https://www.fda.gov/media/137564/download

The official listing of the Inclusion Criteria for Remdesivir https://web.archive.org/web/20201020111539/https://www.va.gov/covidtraining/docs

/20200618 Dynamic Drugs in the Battle of COVID 19/Remdesivir Emergency Use Authorization Requirements.pdf is:

The patient meets at least one of the following: need for mechanical ventilation, extracorporeal membrane oxygenation (ECMO), supplemental oxygen, or room air O_2 saturation \leq 94% YES NO

- 23. On May 14, 2020, the first Mayo Clinic safety paper (not a Phase I Clinical Trial as it was Expanded Access) was reported:
 - Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompas AM, Wiggins CC, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Buskirk CMV, Winters JL, Stubbs JR, Paneth NS, Casadevall A: Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. MedR_xiv Preprint May 12, 2020. https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1.full.pdf
- 24. On May 14, 2020, Dr. Jay Epstein who was 22 years in the Biologics section of the FDA publishes: Epstein J, Burnout T: Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. Vox Sanguinis (2020) 115: 485-487. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7264781/pdf/VOX-9999-na.pdf
- 25. On May 28, 2020, Dr. Jay Epstein published a second paper: Epstein J, Smid M, Wendel S, Somuah D, Burnout T: Use of Covid-19 Convalescent plasma in low-and middle-income countries: a call for ethical principles and the assurance of quality and safety. https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC7283681&blobtype=pdf Published as a commentary in VoxSanguinis (2021) 116, 13-14. https://onlinelibrary.wiley.com/doi/epdf/10.1111/vox.12964
- 26. On June 2, 2020, the European Blood Alliance of 20 countries announces COVID-19 convalescent plasma collection drive. European Blood Alliance: Convalescent Plasma. https://europeanbloodalliance.eu/activities/convalescent-plasma-cpp/
 - European Blood Alliance: Convalescent plasma (CCP). What is COVID-19 Convalescent Plasma (CCP). https://europeanbloodalliance.eu/activities/convalescent-plasma-cpp/
- 27. On June 3, 2020, Drs. Casadevail, Joyner, Pirosfki publish: Casadevail A, Joyner MJ, Pirosfki LA: A randomized trial of convalescent plasma for COVID-19 -- Potentially hopeful signals. JAMA. June 3, 2020: E1 E3. https://pubmed.ncbi.nlm.nih.gov/32492105/; August 4, 2020; 324 (5): 455-457. https://jamanetwork.com/journals/jama/fullarticle/2766940

28. On June 10, 2020, a Turkish review article published reiterating the FDA's insistence in the provision of COVID-19 convalescent plasma late-in-the-disease criteria:

Yigenoglu TN, Hacibekiroglu T, Berber I, Dal MS, Basturk A, Namdaroglu S, Korkmaz S, Ulas T, Dal T, Erkurt MA, Turgut B, Altuntas F: CONCISE REVIEW Convalescent plasma therapy in patients with COVID-19. J Clin Apher 2020; 35: 367-373. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jca.21806

29. Identifying that for the best success implementation of COVID-19 convalescent plasma, it is important that it be given early in the viremic stage of COVID-19. In addition to submitting to Drs. Fauci and Hahn and President Trump, I submitted on June 8, 2020 to the U.S. Copyright Office of the Library of Congress the following:

Andrus CH: Time: The Crucial Independent Variable of the COVID-19 Pandemic, U.S. Copyright Office, Library of Congress, 2020-06-08, Txu002199029. https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=9&ti=1,9&Search%5FArg=Andrus%20Charles%20H&Search%5FCode=NALL&CNT=25&PID=DvTGOW_Qvd_foYxTFrVcdewL3ktMCwz&SEQ=20210425193720&SID=1

30. One week later, White House Press secretary McEnany on June 19, 2020 stated:

...Finally, well second, to finally, we are encouraged that we continue to gather positive data on a number of therapeutics: heparin; dexamethasone or steroids as it's more commonly known; convalescent plasma; and Remdesivir have all shown promise in treating coronavirus. Preliminary findings in a large UK-based recovery trial found that when steroids were used there was a 30% reduction in death for coronavirus patients on ventilators. The FDA is reviewing this recovery trial data now. Additionally, on convalescent plasma there's more encouraging news in partnership with mayo clinic the Trump administration move very quickly on this therapy and it's earliest days recognizing that it showed promise. Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promising--this has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages. The lead investigator of this Mayo Clinic study, Dr. Michael Joyner, summed up his work in saying that convalescent plasma "continues to look promising" noting the "excellent news of this study which covered a diverse population of patients about 20% were African-American, nearly 35% Hispanic, 5% Asian, and 40% women. Prior experience with respiratory viruses and some data that have emerged globally suggest convalescent plasma has the potential to lessen the severity or shorten the length of the illness caused by COVID-19. The results from the Mayo underscore that promise. As you can see, the Trump administration and FDA led on identifying convalescent plasma as a therapeutic and the results are encouraging...

McEnany K: White House Press Conference, June 19, 2020. https://www.youtube.com/watch?v=GxX6CgI7RJ4

31. On June 28, 2020, Secretary Azar makes a plea for donations of COVID-19 Convalescent Plasma: Stracqualusi V: 'Window is closing' for US to get coronavirus under control,

Trump's HHS secretary warns. CNNpolitics, Jun 28, 2020. https://www.cnn.com/2020/06/28/politics/hhs-alex-azar-coronavirus-rise-in-cases-cnntv/index.html

32. On July 7, 2020, an article outlying bradykinin involvement in the late pathophysiology of COVID-19 is published.

Garvin MR, Alvarez C, Izaak Miller J, Prates ET, Walker AM, Kirtley Amos B, Justice A, Aronow B, Jacobson D: A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. eLife, Jul 7, 2020; 1-16 pages. https://elifesciences.org/articles/59177 Copied *verbatim* are from pertinent sections of this very important article on the pathophysioiology of the inflammatory storm which is relatively (>8 days) late component of COVID-19 pathologic symptomatology versus the earlier viremic phase (0 to ~8 days).

Abstract

Neither the disease mechanism nor treatments for COVID-19 are currently known. Here, we present a novel molecular mechanism for COVID-19 that provides therapeutic intervention points that can be addressed with existing FDA-approved pharmaceuticals. The entry point for the virus is ACE2, which is a component of the counteracting hypotensive axis of RAS. Bradykinin is a potent part of the vasopressor system that induces hypotension and vasodilation and is degraded by ACE and enhanced by the angiotensin1-9 produced by ACE2. Here, we perform a new analysis on gene expression data from cells in bronchoalveolar lavage fluid (BALF) from COVID-19 patients that were used to sequence the virus. Comparison with BALF from controls identifies a critical imbalance in RAS represented by decreased expression of ACE in combination with increases in ACE2, renin, angiotensin, key RAS receptors, kinogen and many kallikrein enzymes that activate it, and both bradykinin receptors. This very atypical pattern of the RAS is predicted to elevate bradykinin levels in multiple tissues and systems that will likely cause increases in vascular dilation, vascular permeability and hypotension. These bradykinin-driven outcomes explain many of the symptoms being observed in COVID-19.

eLife digest

In late 2019, a new virus named SARS-CoV-2, which causes a disease in humans called COVID-19, emerged in China and quickly spread around the world. Many individuals infected with the virus develop only mild, symptoms including a cough, high temperature and loss of sense of smell; while others may develop no symptoms at all. However, some individuals develop much more severe, life-threatening symptoms affecting the lungs and other parts of the body including the heart and brain.

SARS-CoV-2 uses a human enzyme called ACE2 like a 'Trojan Horse' to sneak into the cells of its host. ACE2 lowers blood pressure in the human body and works against another enzyme known as ACE (which has the opposite effect). Therefore, the body has to balance the levels of ACE and ACE2 to maintain a normal blood pressure. It remains unclear whether SARS-CoV-2 affects how ACE2 and ACE work.

When COVID-19 first emerged, a team of researchers in China studied fluid and cells collected from the lungs of patients to help them identify the SARS-CoV-2 virus. Here, Garvin et al.

analyzed the data collected in the previous work to investigate whether changes in how the body regulates blood pressure may contribute to the life-threatening symptoms of COVID-19.

The analyses found that SARS-CoV-2 caused the levels of ACE in the lung cells to decrease, while the levels of ACE2 increased. This in turn increased the levels of a molecule known as bradykinin in the cells (referred to as a 'Bradykinin Storm'). .Previous studies have shown that bradykinin induces pain and causes blood vessels to expand and become leaky which will lead to swelling and inflammation of the surrounding tissue. In addition, the analyses found that production of a substance called hyaluronic acid was increased and the enzymes that could degrade it greatly decreased. Hyaluronic acid can absorb more than 1,000 times its own weight in water to form a hydrogel. The Bradykinin-Storm-induced leakage of fluid into the lungs combined with the excess hyaluronic acid would likely result in a Jello-like substance that is preventing oxygen uptake and carbon dioxide release in the lungs of severely affected COVID-19 patients. Therefore, the findings of Garvin et al. suggest that the Bradykinin Storm may be responsible for the more severe symptoms of COVID-19.

Further experiments identified several existing medicinal drugs that have the potential to be repurposed to treat the Bradykinin Storm. A possible next step would be to carry out clinical trials to assess how effective these drugs are in treating patients with COVID-19. In addition, understanding how SARS-Cov-2 affects the body will help researchers and clinicians identify individuals who are most at risk of developing life-threatening symptoms.

Introduction

The COVID-19 beta-coronavirus epidemic that originated in Wuhan, China in December of 2019 is now a global pandemic and is having devastating societal and economic impacts. The increasing frequency of the emergence of zoonotic viruses such as Ebola, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) (among others) are of grave concern because of their high mortality rate (10%–90%). Fortunately, successful containment of those pathogens prevented global-scale deaths. In contrast, the current estimates of mortality for COVID-19 are much lower (~4%), but the virus has now infected more than nine million people and caused nearly a half a million deaths. The cause of mortality appears to be heterogeneous and although it typically targets older individuals, younger individuals are also at risk. A key to combating the pandemic is to understand the molecular basis of COVID-19 that may lead to effective treatments.

Paradoxically, an opportunity that was unavailable with SARS, MERS or Ebola has arisen because of the intense, globally distributed focus of medical and scientific professionals on COVID-19 that is providing a wealth of highly diverse information and data types. Nine bronchoalveolar lavage (BAL) samples were originally collected from patients in Wuhan China for RNA sequencing in order to determine the etiological agent for COVID-19 and resulted in the sequence of the first SARS-CoV-2 viral genome. However, the human reads from these samples were discarded 3. Here, we analyze the human RNA-seq data from these BAL samples alongside 40 controls.

Results and Discussion

The Renin Angiotensin System (RAS)

Although pre-existing hypertension is a reported comorbidity for COVID-19, recent reports indicate hypotension is highly associated with COVID-19 patients once in the hospital (Rentsch, 2020). The RAS is an important pathway linked to these conditions because it maintains a

balance of fluid volume and pressure using several cleavage products of the peptide angiotensin (AGT) and their receptors (Arendse et al., 2019, Flores-Muñoz et al., 2011, Carey, 2017). The most well-studied peptide is angiotensin II (Ang II), which typically generates vasoconstriction and sodium retention via the AGTR1 receptor and vasodilation and natriuresis when binding to the AGTR2 receptor. The RAS also includes several other lesser known peptides that are highly important; Ang1-7 binds to the MAS1 receptor, generating anti-inflammatory and vasodilatory effects, and Ang1-9 binds to the AGTR2 receptor. Ang II is produced by the enzyme ACE whereas Ang1-7 is generated by the combination of ACE and ACE2 activity and Ang1-9 by ACE2 alone. It is important, therefore, to consider all of these components in the context of the others and not any one in isolation.

ACE2 is also the main receptor for the SARS-CoV-2 virus and is not highly expressed in normal lung tissue based on the Genotype-Tissue Expression (GTEx, gtexportal.org) six population. However, results from our differential gene expression analysis of RAS genes in cells taken from BAL samples from individuals presenting with severe symptoms of COVID-19 (Zhou et al., 2020) demonstrates upregulation of ACE2 (199 fold) and disruption of this system compared to controls. In the COVID-19 samples, AGT (34 fold) and the enzyme that activates it (REN, 380 fold) are increased compared to controls whereas the enzymes that produce most of the cleavage products, including ACE (–8 fold), are downregulated, which will likely result in a shift of the entire RAS to produce Ang1-9. In addition, the AGTR1 (430 fold) and AGTR2 (177 fold) receptors are upregulated in BAL COVID-19 samples.

Given the central role that the angiotensin and bradykinin (BK) peptides play in COVID-19 based on our gene expression analysis from BAL samples, we next focused on the RAS- and BK-related gene pathways in lung tissue from the GTEx population; specifically, the networks of genes that are correlated and ani-correlated with the expression of the angiotensin receptors AGTR2 and AGTR1. This subset of genes was annotated with functional information and cell type involvement which resulted in a network (Figure 1) that, as would be expected, demonstrates their extensive involvement in arterial and vascular resistance and blood flow via microvascular dilation, flow, and fluid balance. The genes on the left side of the network are extensively involved in vasoconstriction and contain, among others, ACE, AGTR1, BDKR2, Nitric Oxide Synthase-1, and -2 (NOS1 and NOS2). The right side of the network is extensively involved in decreased arteriolar resistance (vasodilation), increased vascular permeabilization, and altered fluid balance and includes, among other genes, ACE2, AGTR2, and the Vitamin D Receptor (VDR). Surprisingly, we find that both sides of the network are also clearly involved in immune system modulation.

Figure 1

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Functionally annotated network of genes involved in the hypertension-hypotension axis whose expression across the GTEx population is correlated and anticorrelated with the AGTR1 and AGTR2 receptors.

When ACE is downregulated and ACE2 and the BK pathway is upregulated in the lungs of COVID-19 patients it leads to the hypotension, vascular permeability, and the Bradykinin Storm that explains much ... see more

The bradykinin system

Although not as widely discussed as angiotensin, BK is another potent regulator of blood pressure and can be considered essentially an extension of the RAS (Schmaier, 2002). Briefly,

similar to the angiotensin peptides, BK is produced from an inactive pre-protein kininogen (either circulating - HMWK or tissue - LWMK) through activation by the serine protease kallikrein (Figure 2A). Kallikrein is represented by a cluster of serine proteases (KLK1-KLK15) on chromosome 19 with different tissue distributions; KLKB1 (on chromosome 4) is normally expressed in the pancreas and is responsible for circulating (plasma) kallikrein. These proteases are inactivated by zinc and several are known co-receptors for viruses including influenza (Kalinska et al., 2016). KLKB1 is activated by FXII of the intrinsic coagulation pathway, which is normally kept in check by the C1-Inhibitor encoded by SERPING1 (Figure 2A). This has the vital ancillary effect of inhibiting the feedback loop of FXII activation by kallikrein (Kaplan and Ghebrehiwet, 2010).

Figure 2

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Critically disrupted RAS and Bradykinin pathways in COVID-19 BAL samples.

(A) Significantly differentially expressed genes: red ovals indicate genes upregulated in COVID-19, blue are downregulated, colors are scaled to the log2-fold-change values for COVID-19. The overall ... see more

Similar to AGTR2 stimulation, BK induces vasodilation, natriuresis, and hypotension upon activation of the BDKRB2 receptor. BK is tightly integrated with the RAS as BK receptor signaling is augmented by Ang1-9, likely by resensitization of the BDKRB2 receptor (Chen et al., 2005; Marcic et al., 1999; Erdös et al., 2002) and also because ACE degrades and inactivates BK. Interestingly, ACE has a higher affinity for BK than it does for AGT (Cyr et al., 2001) and therefore under conditions where ACE is low, the vasopressor system is tilted toward a BK-directed hypotensive axis (Figure 2A). In addition to its role in pressure and fluid homeostasis, BK is a normal part of the inflammatory response after injury and acts to induce pain via stimulation of the BDKRB1 receptor by BK1-8 (Jacox et al., 2014), which also causes neutrophil recruitment and increases in vascular permeability (Stuardo et al., 2004; Araújo et al., 2001; Hofman et al., 2016; Figure 2B). BK1-8 is produced by the enzyme carboxypeptidase N (CPN1 671 fold) acting on BK.

As with the RAS, the BK system is also severely affected in the COVID-19 BAL samples. The expression of the BK precursor kininogen and nearly all of the kallikreins are undetected in controls but expressed in COVID-19 BAL (Figure 2A). Most of the enzymes that degrade BK, including ACE, are downregulated (–8 fold) in COVID-19 BAL compared to controls, directing BK1-9 and BK1-8 to the upregulated receptors BKB2R (207 fold) and BKB1R (2945 fold), respectively. Of note, the pain-receptor BKB1R is normally tightly controlled and expressed only at very low levels in nearly all tissues in GTEx, but in the case of COVID-19 BAL, both BK receptors are expressed whereas they are virtually undetected in controls. Finally, F12 is unchanged but the SERPING1 (–33 fold) gene that encodes the C1-Inhibitor that inhibits FXII is highly downregulated, which would result in even further increases in BK in COVID-19 patients given its role in KLKB1 activation (Schmaier, 2016). As described below, the resulting Bradykinin Storm is likely responsible for most of the observed COVID-19 symptoms.

Hyaluronic Acid synthesis and degradation

Hyaluronic acid (HA) is a polysaccharide found in most connective tissues. HA can trap roughly 1000 times its weight in water (Cowman and Matsuoka, 2005) and when bound to water the resulting hydrogel obtains a stiff viscous quality similar to 'Jello' (Necas et al., 2008). HAS1, HAS2 and HAS3 are genes that encode hyaluronan synthases which are integral membrane proteins responsible for HA production (Necas et al., 2008). HA is degraded by hyaluronidases encoded by

HYAL1 and HYAL2. Proteins encoded by other genes in this family (HYAL3 and HYAL4) do not appear to have a hyaluronidase activity (Harada and Takahashi, 2007; Kaneiwa et al., 2010). HYAL1 encodes a lysosomal hyaluronidase (Hyal-1) active at low pH and is responsible for intracellular degradation of HA (Harada and Takahashi, 2007). HYAL2 encodes a membrane-bound hyaluronidase (Hyal-2) responsible for extracellular degradation of HA (Harada and Takahashi, 2007). Both Hyal-1 and Hyal-2 are dependent on CD44 (an HA receptor) for activity (Harada and Takahashi, 2007).

As with the RAS and BK systems, the genes encoding HA synthesis and degradation are also severely affected in the COVID-19 BAL samples. There is significant upregulation of the genes involved in HA synthesis: HAS1 (9113 fold), HAS2 (493 fold), and HAS3 (32 fold). The CD44 gene that encodes the HA receptor required for HA degradation and the gene encoding extracellular hyaluronidase HYAL2 are both downregulated (–11 and –5 fold respectively) in the BAL fluid of COVID-19 patients. HYAL1 is not expressed in the BAL fluid of controls or the COVID-19 patients. The result of these shifts in expression would be likely to cause an increase in the amount of HA in the bronchoalveolar space of the lungs which, combined with the vascular hyperpermeability caused by BK, could form a viscous hydrogel that would negatively impact gas exchange (Figure 3). In fact, HA in BAL fluid has previously been associated with acute respiratory distress syndrome (ARDS) where there was a significant anticorrelation between the concentration of HA and the pulmonary oxygenation index (Modig and Hällgren, 1989; Hällgren et al., 1989). HA has also been associated with pulmonary thrombosis and/or ground glass opacities in radiological findings (Bhagat et al., 2012; Han et al., 2019; Jang et al., 2014).

Figure 3

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The upregulation of hyaluronan synthases and downregulation of hyaluronidases combined with the BK-induced hyperpermeability of the lung microvasculature leads to the formation of a HA-hydrogel that inhibits gas exchange in the alveoli of COVID-19 patients.

Although not the focus of the present study, coagulopathy is commonly reported in cases of COVID-19 (The Lancet Haematology, 2020), and there are suggestions in the literature of links between RAS and coagulopathy. The Ang1-9 peptide that is increased in COVID-19 BAL stimulates thrombosis by inhibiting fibrinolysis (Mogielnicki et al., 2014). In addition to BK, ACE also degrades the antifibrotic peptide N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), which is produced from thymosin beta-4 (TMSB4X, -130 fold) (Kanasaki, 2020). Increased fibrinolysis could therefore be achieved by increasing ACE, or by administering thymosin beta-4, which is currently in clinical trials for the treatment of cardiovascular disorders (Timbetasin). If TMSB4X is, in fact, protective, it could explain the lower incidence of COVID-19 induced mortality in women (Jin et al., 2020) because it is found on the X chromosome and escapes X-inactivation. Women therefore would have twice the levels of this protein than men, which is supported by our BAL analysis (–207 fold in males, –131 fold in females).

In addition, both the RAS and BK pathways have previously been tied to HA. It was found that Angiotensin II increased CD44 expression and hyaluronidase activity (Bai et al., 2016). As discussed above, COVID-19 likely significantly downregulates the production of Angiotensin II which is consistent with the decrease in CD44 expression that is seen in the BAL fluid of SARS-CoV-2 infected patients. Furthermore, IL2 was recently reported to be highly upregulated in symptomatic but not asymptomatic COVID-19 patients (Long et al., 2020; Paegelow et al., 1995; Mustafa et al., 2002) and is upregulated (21 fold) in the BAL samples compared to controls.

This cytokine is induced by BK in the lung, and causes vascular leakage syndrome (VLS), which appears to be mediated through CD44. Interestingly, CD44 knockout mice displayed reduced IL2-induced VLS, suggesting this may be a valuable target for COVID-19 intervention.

Clinical description of COVID-19

According to the CDC, the majority of SARS-CoV-2 infections are asymptomatic or mild. Those that proceed to more severe forms present with fever, a non-productive cough that may result in hemoptysis and shortness of breath. Other common symptoms are myalgia, fatigue, sore throat, nausea, vomiting, diarrhea, conjunctivitis, anorexia, and headache (cdc.gov/coronavirus/2019ncov/hcp/clinical-guidance-management-patients.html). Reports from blood studies include leukopenia, eosinopenia, neutrophilia, elevated liver enzymes, C-reactive protein, and ferritin (Fan et al., 2020; Huang et al., 2020; Goyal et al., 2020). Furthermore, autopsies have reported extensive hyaline membrane formation in the lungs of COVID-19 patients (Barton et al., 2020; Xu et al., 2020; Adachi et al., 2020; Mong et al., 2020). Specifically, histological analysis of the lungs of a deceased COVID-19 patient showed organizing hyaline membranes in the early stages of alveolar lesions and prominent hyaline membranes in the exudative phase of diffuse alveolar damage (Adachi et al., 2020). In a seperate post mortem study of lung tissue from COVID-19 patients, microscopic examination found 'numerous hyaline membranes without evidence of interstitial organization' (Barton et al., 2020). Furthermore, in another autopsy study of a COVID-19 patient, histological analysis found extensive hyaline membranes, which the authors interpreted as indicative of ARDS (Xu et al., 2020). Finally, a meta-analysis showed that there was a statistically significant 4.6 fold difference in lung weight of COVID-19 patients versus controls, which they conclude is consistent with the HA-hydrogel formation known to occur in ARDS (Mong et al., 2020).

Although much focus has been on the lung due to the need for ventilator support of end-stage disease, COVID-19 also affects the intestine, liver, kidney, heart, brain, and eyes (Wadman, 2020). Nearly one-fifth of hospitalized patients experience cardiac injury (Shi et al., 2020), many of whom have had no history of cardiovascular problems prior to infection. Responses include acute myocardial injury, myocarditis, and arrhythmias (Driggin et al., 2020) that may be due to viral infection directly, which is consistent with high expression of the SARS-CoV-2 receptor ACE2 in cardiac tissue (gtexporta.org). An important extension of the RAS in controlling cardiac contraction and blood pressure is the potent inotrope apelin (APLN), which acts as an NO-dependent vasodilator when its receptor (APLNR) heterodimerizes with BDKRB1 (Bai et al., 2014). APLN (98 fold), APLNR (3190 fold) and BDKRB1 (2945 fold) are all upregulated in COVID-19 BAL. As with BK and ANG derived peptides, APLN is inactivated by Neprilysin (MME), which is significantly downregulated in the BAL samples from COVID-19 individuals (–16 fold). Therefore, increased APLN-signaling can be added to the imbalanced RAS.

In addition to cardiac dysfunction, neurological involvement in COVID-19 was revealed after an MRI assessment of COVID-19-positive patients with encephalopathy symptoms in France identified enhancement in leptomeningeal spaces and bilateral frontotemporal hypoperfusion (Helms et al., 2020) which are consistent with increased vascular permeabilization in the brain. Furthermore, earlier reports from China indicate high frequencies of dizziness, headache, as well as taste and smell impairment (Mao et al., 2020). The most recent reports from the United States and China indicate that 30–50% of COVID-19 patients experience adverse gastrointestinal symptoms (Cholankeril, 2020; Pan et al., 2020). Direct infection by the virus and damage to the kidney was also observed, specifically in the proximal tubules (Su et al., 2020). These latter two findings are not surprising given the higher expression of ACE2 in these tissues compared to tissues overall (gtexportal.org), which would facilitate infection by the virus. Finally, COVID-19

patients also frequently display skin rashes including 'covid-toe' that appear to be related to dysfunction of the underlying vasculature.

Bradykinin Storms: A model of SARS-CoV-2, COVID-19, and BK-driven Vascular Permeabilization

Based on previous work in SARS-CoV-1 and SARS-CoV-2, it is likely that this new coronavirus enters host cells in nasal passages where the receptor ACE2 is moderately expressed. Migration to throat tissues and passage through the stomach is then possible given that SARS-CoV-2 can survive the extreme pH of the gastric tissues (Chin et al., 2020) and infection could then expand into the intestines where ACE2 levels are high (GTEx Consortium, 2013). Initial infection might not occur in the lung epithelium given that ACE2 is undetectable or expressed at extremely low levels there (GTEx Consortium, 2013). Following infection, the single polypeptide that is translated from the virus' positive-strand RNA genome is cleaved into active proteins by the non-structural protein 3CLpro protease. This protein is then repurposed by the virus to inactivate the host cells' first line of defense, interferon, most likely by degrading the NFkappaB activating factor IKK-gamma as has been shown to happen in the porcine coronavirus PEDV (Wang et al., 2016).

Aside from self-protection, the suppression of NFkappaB (–9 fold reduced in BAL samples) directly affects the RAS as NFkappaB normally induces the expression of ACE by binding to its promoter and increasing transcription (Garcia et al., 2016; Figure 2A). This likely relates to the role of ACE in the innate immune response that is independent of its actions on the vascular system (Bernstein et al., 2018). The virus therefore acts pharmacologically as an ACE inhibitor by reducing its RNA expression more than 10-fold, which is supported by our BAL RNA-seq analysis. Additionally, ACE2 expression is normally downregulated in-part by Ang II (Patel et al., 2016). As Ang II is the catalytic product of ACE, it would seem that the virus's ability to decrease ACE expression would have the effect of upregulating ACE2 (199 fold in our BAL analysis). In some patients, severe pulmonary involvement could occur when the virus is introduced into the intestinal lymph vessels and moves up the lymphatic system (Chen, 2020), enters the bloodstream at the thoracic duct and moves through the heart and into the lung microvasculature where it could attack cells in the lungs that now express ACE2 due to virus-induced upregulation.

Given that the high levels of ACE in the vascular bed of the lung are the major producer for circulating angiotensin-derived peptides (Studdy et al., 1983), establishment of SARS-CoV-2 in the lung will have profound effects. Downregulation of ACE here (confirmed in BAL samples from COVID-19 patients) will result in the diversion of the RAS to produce the BK-augmenting peptide Ang1-9, exacerbating BK-effects, such as pain sensitization and increased vascular permeability on a system-wide level. Expansion of this imbalance as described above (Figure 2), increases levels of BK and will result in increased vascular permeability in tissues that have been infected by SARS-CoV-2 and be most severe in those that are normally regulated by ACE. ACE may also provide a key diagnostic point as half of the variation amongst individuals can be explained by an insertion/deletion polymorphism of the gene (Rigat et al., 1990).

As mentioned above, the combination of vascular permeability and HA build up in the lungs could produce a hydrogel that significantly inhibits gas exchange in bronchoalveolar spaces. This is consistent with the autopsy reports of hyaline membranes in the lungs of deceased COVID-19 patients as well as other acute respiratory distress conditions (e.g., SARS, MERS, ARDS) (Barton et al., 2020; Xu et al., 2020; Adachi et al., 2020) Although this likely represents a late-stage event in severe cases of COVID-19, if the cause is overproduction of HA as a result of disruption of the

RAS, it is also a potentially valuable intervention point because the condition is easily identified, and treatment could have rapid and significant beneficial effects.

In addition, increased levels of the vasodilating peptide APLN that are produced in COVID-19 patients could have spillover effects on cardiac function. APLN upregulates the expression of ACE2 (Sato et al., 2013) and directly affects cardiac contraction and vasodilation. Increased levels of APLN are known to be associated with cardiac arrhythmia (Salska et al., 2018) and in the case of hyper-stimulated BK output, could be causing cardiac events in COVID-19 patients. In addition, increased levels of APLN could lead to more ACE2 receptors for SARS-CoV-2 in the heart and thus stimulate further infection.

Furthermore, excess BK can lead to hypokalemia (Zhang et al., 2018), which is associated with arrhythmia and sudden cardiac death (Kjeldsen, 2010), (Bielecka-Dabrowa et al., 2012; Skogestad and Aronsen, 2018), both of which have been reported in COVID-19 patients (Huang et al., 2020; Guo et al., 2020), (Wang et al., 2020); a recent report confirms that hypokalemia is occurring in severe cases of COVID-19 (Lippi et al., 2020). It is also notable that many of the other symptoms being reported for COVID-19 (myalgia, fatigue, nausea, vomiting, diarrhea, anorexia, headaches, decreased cognitive function) are remarkably similar to other hyper-BK-conditions that lead to vascular hyper-permeabilization such as angioedema as was recently noted (van de Veerdonk et al., 2020). In agreement with that report, our results indicate that the pathology of COVID-19 is likely the result of Bradykinin Storms rather than cytokine storms (although given the induction of IL2 by BK, the two may be intricately linked). This model predicted that a loss of ACE2 would exacerbate the BK-induced pathogenesis (van de Veerdonk et al., 2020). However, the BAL fluid expression data indicate that the Bradykinin Storm is instead caused by upregulation of ACE2 and reduced degradation of BK by ACE. Based on this data-driven model, an individual's symptomatology is likely directly related to the specific tissue distribution of viral infection around the body (Figure 4) and should be viewed in the context of an overactive bradykinin response. The majority of circulating BK is degraded in the lungs by ACE and therefore heterogeneous symptoms of COVID-19 could also be the result of systemic effects of increased levels of circulating bradykinin and the eight-fold reduction of ACE in the lung microvasculature that would normally degrade it.

Figure 4

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Systemic-level effects of critically imbalanced RAS and BK pathways.

The gene expression patterns from COVID BAL samples reveal a RAS that is skewed toward low levels of ACE that result in higher levels of Ang1-9 and BK. High levels of ACE normally present in the ... see more

Given this model, factors that affect RAS balance should be further investigated in the framework of diagnosis and treatment. For example, another well-documented regulator of RAS is Vitamin D (Vaidya and Williams, 2012) as the liganded Vitamin D receptor (VDR) suppresses REN expression. Patients who are deficient in Vitamin D are at-risk for ARDS in general (Dancer et al., 2015) and Vitamin D deficiencies have recently been associated with severity of illness in COVID-19 patients (Alipio, 2020). Our BAL gene expression analysis shows that VDR is 2-fold down-regulated and enzymes [CYP24A1 (465 fold), CYP3A4 (208 fold)] that catabolize Vitamin D (1,25(OH)2D) and its precursor (25OHD) (Bikle, 2014) are up-regulated in COVID-19 patients compared to controls, which will likely result in further increases in REN. Furthermore, our analysis of ChipSeq experiments from a VDR study Tuoresmäki et al., 2014 have determined that,

in addition to REN, the following genes in the RAS-Bradykinin system have a VDR binding site within 20 kilobases: BDKRB1, BDKRB2, CYP24A1, DPP4, IKBKG (regulates NFkappaB), KLK1, KLK2, KLK4, KLK6, KLK7, KLK9, KLK10, and MME. Six of these binding sites can be tied to the following genes via chromatin structure with the use of H-MAGMA and Hi-C data (see Materials and methods): DPP4, BDKRB2, KLK6, KLK7, KLK10, and IKBKG. VDR binds to many sites in the genome with tissue-specific binding patterns so these putative associations to other genes in the RAS and BK pathways will require further investigation.

Potential interventions

Several interventional points (most of them already FDA-approved pharmaceuticals) could be explored with the goal of increasing ACE, decreasing BK, or blocking BK2 receptors (Table 1). Icatibant is a BKB2R antagonist (Dubois and Cohen, 2010) whereas Ecallantide acts to inhibit KLKB1, reducing levels of BK production (Farkas and Varga, 2011). Androgens (danazol and stanasolol) increase SERPING1, although the side effects likely make these undesirable (Wilkerson, 2012), but recombinant forms of SERPING1 (Berinert/Cinryze/Haegarda) could be administered to reduce BK levels. It should be noted that any intervention may need to be timed correctly given that REN levels rise on a diurnal cycle (Gordon et al., 1966), peaking at 4AM which corresponds with the commonly reported worsening of COVID-19 symptoms at night. Another approach would be the modulation of REN levels via Vitamin D supplementation when warranted. 4-methylumbelliferone (Hymecromone) is a potent inhibitor of HAS1, HAS2, and HAS3 gene expression and results in the suppression of the production of hyaluronan in an ARDS model (McKallip et al., 2003; McKallip et al., 2013). Hymecromone (4-methylumbelliferone) is approved for use in Asia and Europe for the treatment of biliary spasm. However, it can cause diarrhea with subsequent hypokalemia, so considerable caution should be used if this were to be tried with COVID-19 patients (NCATS Inxight, 2020). As mentioned above, Timbetasin may reduce COVID-19 related coagulopathies by increasing fibrinolysis.

Table 1

Potential therapeutic interventions, their targets, and predicted effect.

Drug	Target	Predicted Effect
Danazol, Stanozolol	SERPING1	Reduce Bradykinin production
Icatibant	BKB2R	Reduce Bradykinin signaling
Ecallantide	KLKB1	Reduce Bradykinin production
Berinert,Cinryze,Haegarda	SERPING1	Reduce Bradykinin production
Vitamin D	REN	Reduce Renin production
Hymecromone	HAS1,HAS2, HAS3	Reduce hyaluronan
Timbetasin	TMSB4X	Increase fibrinolysis

The testing of any of these pharmaceutical interventions should be done in well-designed clinical trials. Given the likely future outbreaks of zoonotic viruses with a similar outcome, it would be in the best interest long-term to invest in the development of small molecules that can inhibit the virus from replicating or suppressing the host immune system such as a 3CLpro inhibitor. However, to date, no large multi-centered, randomized, placebo controlled, blinded clinical trials have been done with 3CLpro inhibitors (Sisay, 2020). In the meantime, our analyses suggest that prevention and treatment centered on vascular hyper-permeability and the suppression of hyaluronan may prove beneficial in fighting the pathogenesis of COVID-19. Given the fact that two recent studies have validated our model's predictions of hypokalemia (Lippi et al., 2020) and Vitamin D deficiency (Alipio, 2020) in COVID-19 patients, we suggest that rapid testing of the pharmaceutical interventions discussed above is warranted.

Decision letter

- Frank L van de Veerdonk Reviewing Editor; Radboud University Medical Center, Netherlands
- .
 - Jos WM van der Meer Senior Editor; Radboud University Medical Centre, Netherlands
- •
- Frank L van de Veerdonk Reviewer; Radboud University Medical Center, Netherlands
- •
- Roger Little Reviewer

In the interests of transparency, eLife publishes the most substantive revision requests and the accompanying author responses.

Acceptance summary:

The manuscript has highlighted a core response in COVID-19 with RAS and bradykinin which is really a different signature than any other viral pneumonia other than coronavirus infection. This supports the importance of these pathways in coronavirus and contributes to a better understanding of COVID-19. The novelty and importance is also the site of infection (the lungs) that has been studied for this signature which really adds novelty to the existing literature.

Decision letter after peer review:

Thank you for submitting your article "A Mechanistic Model and Therapeutic Interventions for COVID-19 Involving a RAS-Mediated Bradykinin Storm" for consideration by *eLife*. Your article has been reviewed by three peer reviewers, including Frank L van de Veerdonk as the Reviewing Editor and Reviewer #1, and the evaluation has been overseen by Jos van der Meer as the Senior Editor. The following individual involved in review of your submission has agreed to reveal their identity: Roger Little (Reviewer #3).

The reviewers have discussed the reviews with one another and the Reviewing Editor has drafted this decision to help you prepare a revised submission.

We would like to draw your attention to changes in our revision policy that we have made in response to COVID-19 (https://elifesciences.org/articles/57162). Specifically, we are asking editors to accept without delay manuscripts, like yours, that they judge can stand as *eLife* papers without additional data, even if they feel that they would make the manuscript stronger. Thus the revisions requested below only address clarity and presentation.

Summary:

The authors have used a systems biology approach and analyzed data from BAL (9 COVID patients) with 40 control BALs. They clearly demonstrate a signature of a dysregulated RAAS and

KKS. Further analysis shows the signature is skewed towards an incapacity to dampen the KKS and bradykinin production that might lead to a bradykinin storm that could contribute to the endothelial dysfunction that results in vascular leakage seen in the early stages of patients admitted to the hospital with COVID. The data are timely, conclusions supported by the data and the BAL sample analysis provides real novel data.

Figure 2: Please designate Figure 2 into two panels: A and B, since it is later refered to in this way in the text. It would also be helpful to illustrate the scale so one can observe the large disruption of the system. The scale only goes to 5 in both directions, and being able to see the extreme over-expression would improve the argument that components of the BK system are overexpressed.

Subsection "Hyaluronic Acid Synthesis and Degradation". It would be helpful to add a sentence of two to expand on the pulmonary thrombosis evidence, as it's known that thrombosis is observed in some Covid-19 patients. It could possibly be added in the third paragraph below.

Subsection "Bradykinin Storms: A Model of SARS-CoV-2, COVID-19, and BK-driven Vascular Permeabilization" third paragraph. The HA hypothesis is compelling and potentially explanatory for the hypoxia observed in Covid-19 patients. This hypothesis would be better supported by a representation of the data referenced here (Barton et al., 2020; Xu et al., 2020; Adachi et al., 2020), as opposed to just stating that HA buildup is observed. Either a discussion or even a table would be useful with referenced data.

Same section paragraph five. Here again, it would be useful to represent the studies mentioned here (van de Veerdonk et al., 2020) with similar phenotypic observations to Covid-19. Additional discussion of the data from that paper, or even better the addition of a table with referenced data is suggested. The BK hypothesis is a strong and central hypothesis of this paper and it would be better supported with more than just a statement and a reference.

The results of the ChipSeq analysis should be further described. Most importantly, what is the significance of the binding site within 20 kilobases? It seems like a lot of genomic real estate to make an assertion that there is some effect. Is there any evidence this proximity results in activation or deactivation? If so please provide a reference.

Subsection "Potential Interventions": Another suggestion here to include a table with suggested interventions -> targets -> drugs -> expected effects.

Supplementary figures S1 and S2 could be represented by single tables and also made available in.xls forms

- 33. On July 7, 2020, Blankenship K: Regeneron bags \$450M deal with U.S. Government for coronavirus antibody cocktail supply. Fierce Pharma. https://www.fiercepharma.com/manufacturing/regeneron-bags-450m-deal-u-s-government-for-covid-19-antibody-cocktail
- 34. On July 9, 2020, Guarascio F: EU raises its bet on blood plasma in search for COVID-19 therapy. Reuters. https://www.reuters.com/article/us-health-coronavirus-eu-

<u>plasma/eu-raises-its-bet-on-blood-plasma-in-search-for-covid-19-therapy-idUSKBN24A1N2</u>

- 35. On July 10, 2020, Gillenwater S, Rahaghi F, Hadeh A; McMahon JH, Udy A, Peleg AY; McCaw ZR, Kim DH, Wei LJ; Olalla J; Beigel JH, Tomashek KM, Dodd LE: Letters to the Editor regarding "Remdesivir for the treatment of Covid-19 Preliminary report." Published July 10, 2020, at NEJM.org and subsequently published N Engl J Med September 3, 2020; 383: 992-994. https://www.nejm.org/doi/pdf/10.1056/NEJMc2022236?listPDF=true
- 36. July 13, 2020, Sharun K, Tiwari R, Yatoo MI, Patel SK, Natesan S, Dhama J, Malik YSS, Harapan H, Singh RK, Dhama K: Antibody-based immunotherapeutics and use of convalescent plasma to counter COVID-19: advances and prospects, Expert Opinion on Biological Therapy, 20:9, 1033-1046, DOI: 10.1080/14712598.2020.1796963

 https://www.tandfonline.com/doi/pdf/10.1080/14712598.2020.1796963?needAccess=true
- 37. On July 19, 2020, the second "safety update" is published from the Mayo Clinic/FDA Expanded Access program in which 20,000 hospitalized patients at the late-stages of COVID-19 are given COVID-19 convalescent plasma. Even though 20,000 patients were administered COVID-19 convalescent plasma safely, this fails to "Complete" as Phase I Clinical Trial as this is Expanded Access/Compassionate Use program. Thus, the Right to Try Law, PL- is circumvented.

Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, Wiggins CC, Senefeld JW, Klompas AM, Hodge DO, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimabal RJ, Bauer PR, Blair JE, van Buskirk CM, Winters JL, Stubbs JR, van Helmond N, Butterfield BP, Sexton MA, Soto JCD, Paneth NS, Verdun NC, Marks P, Casadevall A, Fairweather D, Carter RE, Wright RS. COVID-19 Convalescent Plasma in 20,000 hospitalized patients. Mayo Clin Proc September 2020; 95(9): 1888-1897. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7368917/pdf/main.pdf

Serious Adverse Events. Key serious adverse events (SAE) related to the transfusion of convalescent plasma are reported in Table 2. Our report is not a comprehensive summary of all risks associated with hospitalization of COVID-19 but did assume that convalescent plasma potentially could cause life-threatening cardiac events and thrombotic events, so these were collected with an underlying assumption of attribution. Within four hours of completion of the COVID-19 convalescent plasma transfusion, 146 SAEs classified as transfusion reactions were reported (<1% of all transfusions). Of these SAEs, there were 83 non-mortality events reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction. Of the SAEs reported within four hours of plasma transfusion, there were 63 mortalities (0.3% of all transfusions) and 13 of these mortalities were judged as related (possibly, n=12; probably, n=1; definitely, n=0) to the transfusion of COVID-19 convalescent plasma. Within seven days of completion of the COVID-19 convalescent plasma transfusion, 1,136 other SAEs were reported. Of these SAEs, 87 thromboembolic or thrombotic events were reported, 406 sustained hypotensive events requiring intravenous pressor support were reported, and 643 patients suffered a cardiac event. Notably, the vast majority of the thromboembolic or thrombotic

complications (n=55) and cardiac events (n=569) were judged to be unrelated to the plasma transfusion.

(Please see Table II: Mayo Clinic Study morbidity, mortality, and odds of dying which is a data base analysis of the results and why the Mayo Clinic "Safety Update" should qualify as a Completed Phase I.)

- 38. On July 22, 2020, in addition to submitting to Drs. Fauci and Hahn and President Trump, I submitted to the U.S. Copyright Office of the Library of Congress: Andrus CH: The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma. U.S. Copyright Office, 2020-07-22, TXu002214049. <a href="https://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=6&ti=1,6&Search%5FArg=andrus%20charles%20h&Search%5FCode=NALL&CNT=25&PID=cXfFuGrmHQvLVILvfNNt7Yjwh73ImgQ&SEQ=20210512081428&SID=1
- 39. On July 30, 2020, President and the White House COVID-19 Commission go to the American Red Cross, Charles Drew, M.D., F.A.C.S. Blood Bank, to highlight the need for COVID-19 convalescent plasma. With all the publicity on that day though, the White House withholds the announcement of the EUA until August 23, 2020, the evening before the Republican National Convention, presumably so as to get a bump in the polls.

American Red Cross: President Trump visits the American Red Cross. To highlight need for convalescent plasma during COVID-19. https://www.redcross.org/about-us/news-and-events/press-release/2020/red-cross-highlights-need-for-convalescent-plasma-during-covid-19.html

Hahn S: Plasma Donation – PSA https://www.youtube.com/watch?v=PIX15rWdBbY

Howard Bauchner, M.D., JAMA Editor-in-Chief, Interview of FDA Commissioner, Stephen Hahn, M.D. https://www.youtube.com/watch?v=UdmaU2-C_wE

McKend E: Dr. Birx: Plasma donations needed as coronavirus cases spike nationwide. https://spectrumnews1.com/ky/lexington/health/2020/07/30/dr--birx--plasma-donations-needed-as-coronavirus-cases-spike-nationwide

FDA: Donate COVID-19 plasma.

http://web.archive.org/web/20200731065328/https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma First attachment of "Dr. Hahn – Plasma Donation – PSA", https://www.youtube.com/watch?v=PIX15rWdBbY [Initially posting April 14, 2020]

40. On August 4, 2020 in the Wall Street Journal, Amy Dockser Marcus reports:

Convalescent plasma reduced death rate among Covid-19 patients, study data signals—
Hospitalized patients who got earlier transfusions of blood plasma rich in antibodies to the coronavirus show a lower mortality rate. Wall Street Journal.

https://www.wsj.com/articles/convalescent-plasma-reduced-death-rate-among-covid-19-patients-study-data-signals-11596594390

Hospitalized Covid-19 patients who received transfusions of blood plasma rich with antibodies from recovered patients reduced their mortality rate by about 50%, according to researchers running a large national study.

The researchers presented their data analysis Saturday in a webinar for physicians interested in learning about so-called convalescent plasma, with data slides that were reviewed by The Wall Street Journal. The researchers said they saw signs that the treatment might be working in patients who received high levels of antibodies in plasma early in the course of their illness. They based their conclusions on an analysis of about 3,000 patients.

Patients who at three days or less after diagnosis received plasma containing high levels of antibodies against the coronavirus had a mortality rate of 6.6% at seven days after the transfusion. That compared with a mortality rate of 13.3% for patients who got plasma with low levels of antibodies at four days or more after diagnosis. That indicates reduced mortality of about 50%, the researchers said.

At 30 days after transfusion, the mortality rate was reduced by about 36%, investigators reported.

41. On August 6, 2020, there were three pertinent articles regarding COVID-19 convalescent plasma:

Bloch EM: Convalescent plasma to treat COVID-19. Convalescent plasma to treat COVID-19. Blood 6 August 2020; 136 (6): 654-655. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414591/pdf/main.pdf

In conclusion, observational studies and compassionate use programs have been instrumental in the mobilization of CCP to contend with a global health emergency. Although safety has been addressed, efficacy data are critically needed to transition CCP's status from an investigational product to a standard therapy. The latter has practical ramifications, offering a formal mechanism for reimbursement and thus durable treatment strategy. Broadly, COVID-19 presents a rare opportunity to study CP. If shown to be effective, CP would offer a scalable model that could be applied both to the current pandemic as well as to future emerging infectious diseases. It could also facilitate development of hyperimmune globulin and vaccine design. Clinical trials are already under way to address the uncertainty of use. Nonetheless, harmonization of efforts is needed along with creative approaches to overcome looming obstacles, such as pairing of trials of similar design and/or metanalysis. We must not be left wondering whether the intervention worked after the pandemic wanes.

On August 6, 2020, Xia, Liu X, Lv T, Gan Z, Chen G, Pan Y, Liu C, Zhang K, Xu X, Wang C, Wang Q: Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood 6 August 2020; 136 (6): 755-758. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414593/pdf/main.pdf

Experience from SARS-CoV-1 shows that convalescent plasma is most effective when administered shortly after symptom onset, typically within 2 weeks.7,14,17 The study by Liu et al¹⁶ showed that the effect of CCP was similar in an interval of 3 weeks' duration of symptoms. We compared the time to clinical improvement in patients with different therapy timings in our

cohort, including 1 to 4 weeks, 5 to 6 weeks, 7 weeks, and \$8 weeks after symptom onset. The results showed that the median time to clinical improvement was ;10 days in the 1 to 4 weeks', 5 to 6 weeks', and 7 weeks' groups. However, the time to clinical improvement was significantly prolonged in the \$8 weeks' group (Figure 1I).

In summary, we analyzed a large cohort of patients with COVID19 who received CCP and provide detailed evidence regarding their clinical improvement. Although the homogeneous data obtained from a single center may reduce some biases, there could inevitably be some confounding factors (eg, biased patient assignments) in this retrospective study. In addition, complete data on neutralizing antibody titers in CCP units were not available, limiting the power of evaluating the correlation between the quality of donor plasma and efficacy. Moreover, a stratified analysis of cases of severe and critical patients could not be performed due to the low proportion of critical patients. This analysis differs from existing studies in that its dynamic laboratory observations using large-scale data make it possible to analyze the potential therapeutic mechanism of CCP, recognize the characteristics of responders and nonresponders, and identify the indications and timing of therapy.18 Our results suggest that CCP, transfused even after 2 weeks (median of 45 days in our cohort) of symptom onset, could improve the symptoms and mortality in patients with severe or critical cases of COVID-19. We anticipate that this study could shed new light in clinical practice and monoclonal antibody development for COVID-19.

Tobian AA, AA, Shaz BH: Earlier the better: convalescent plasma. Blood 6 August 2020; 136(6): 652-653.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414595/pdf/main.pdf

Convalescent plasma is one of the best therapies currently available to treat COVID-19. However, critical questions on timing of treatment in the disease course and dose (volume and antibody titer levels) need to be answered. These answers will also help prepare us for other passive antibody treatments (eg, hyperimmune globulin made from convalescent plasma and monoclonal antibodies). The medical community must work together to battle this deadly disease in order to determine the best therapies and reduce mortality.

42. On August 12, 2020, when a St. Louis Post-Dispatch reporter asked why there had been a failure in patient recruitment in prospective randomized studies of CCP and why patients would theoretically agree to participation in a prospective, placebo-controlled study in the opinion of the researcher being questioned. [The answer to the question below quoted by the reporter is suggestive of coercion in Medical Research and should not be tolerated by any Institutional Review Board (IRB)] (aside: The U.S. Federal Government Statutory Oversight of all IRBs in this country is the U.S. Food and Drug Administration. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/institutional-review-boards-irbs-and-protection-human-subjects-clinical-trials Unfortunately, such FDA oversight regarding a specific IND or INE has the potential of being an inherent conflict-of-interest. During the COVID-19 pandemic, the complete involvement of the NIH and the FDA may have been akin to The fox guarding the hen house!)]:

Kozlov M: Two Washington U. doctors lead national effort to study new COVID-19 treatment. St. Louis Post-Dispatch Aug 12, 2020.²⁹¹ https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article ccec0f56-4493-5a26-8601-45e35d364b2d.html

Since April, the Trump administration has set aside **more than \$300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving highrisk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

The existence of the IRBs are the epitomization of the prohibition of coercion (or implied coercion) in Medical Research on Human Subjects as professed in the Nuremburg Code, the Helsinki Accords, and the Belmont Report; but there has been much controversy over when the ethical line(s) are crossed. 18,26,28,29,31,49,62,64,72,83,131,328,383,413,492,510,531,532,537

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26.0 13.0

2021-06-27 Passive Immunization has been around for 135 years!

150 Emerald Green Ct St. Louis, MO. 63141 June 27, 2021 (314) 455-9482

President Joseph Biden
President of the United States of America
The White House
1600 Pennsylvania Avenue
Washington, D.C.
202-456-1414

Re: NIAID Case #12276: On March 24, 2020 going forward, the FDA, the NIH, and *The White House* abandoned the USA Public by restricting COVID-19 Convalescent Plasma (CCP) from anyone early-in-the-course of COVID-19 viremia

Dear Mr. President,

Fifteen months ago I began writing Dr. Fauci, Dr. Hahn, and President Trump advocating for the **EARLY** *Passive Immunization* treatment of Convalescent Plasma against COVID-19. Naively quoting to them from Dorothy Haas' children's reader: Men of Science³ President Trump, Dr. Fauci, and I--and yourself—grew up in the 1950s and 60s when knowledge of the mandatory early treatment of individuals bitten by rabid animals with the rabies vaccine was commonknowledge. I naïvely assumed that American Medicine would hit upon using COVID-19 convalescent plasma early in the course-of-the-disease in the treatment of all individuals infected with COVID-19 early during the viremic phase —BUT, I was wrong! Louis Pasteur's listening to the desperate plea of Mrs. Meister for her nine-year-son, Joseph, and his subsequent (overnight decision) acting upon it with 21 daily abdominal wall injections of rabbit emulsified spinal tissue containing rabbit antibodies against rabies was an early successful utilization of *Passive Immunization* in humans. That one anecdotal report--which is contrary to today's professed sanctity of the "Evidenced-Based-Medicine deity"--changed the course of history. In 1901, the first Nobel Prize in Physiology or Medicine was awarded to **Emil von Behring** for his work on serum therapy = *Passive Immunization*. For over a century, Passive Immunization has been key in the initial medical addressing of emerging viral and bacterial epidemics in which we did not or do not have pharmaceutically produced antivirals, antibiologics, antibiotics, and/or agents of Active Immunization (vaccines). Even in SARS-1, Ebola, and Zika, Passive Immunization in the form of convalescent plasma and monoclonal antibodies have proven effective. https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo002465&aid=10.1056 %2FNEJMp1802256&area= Over the last 15 months, though, we have minimized during our panic regarding COVID-19 by misinformation, public misdirection, and discrediting the utility of Passive Immunization and, as society, have "gotten stuck" among the first 4 stages of Kübler-Ross' *On Death and Dying*.

This is a story that encouraged self-promoting individuals in very high places who advocated and advanced for their own personal agendas the discrediting of any immediate treatment with

Passive Immunization by misinformation, misdirection, arrogance, greed, and most-of-all, inhumanity to their fellow man. With little Clinical Leadership or Direction regarding the care of the individual patient, COVID-19 pathophysiology was minimized or ignored with the avoidance of **early** treatment during the viremic phase of COVID-19. This is a story in which previous history was discounted and minimized in the **early** treatment of an emerging viral epidemic. This was time when by legal obfuscation American Medicine and our Government covered-up and bureaucratically redefined Federal definitions; overwrote previous directives and policies (without officially rescinding prior documentation) thus burying policies only days old, and indirectly avoided and violated the intent of such Federal laws as PL-115-176, The Right to Try Act. This is a tragedy in which moral standards regarding human experimentation were set aside or ignored violating the tenants of such historical guideposts as the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. Most-of-all, the last 15 months have seen a complete blurring of the separation of human research and experimentation with the inherent conflict-of-interest of industry-directed Medical research centered around financial self-interest, business advancement, and corporate greed.

Mr. President, please read the summary article that follows and the abridged information that has previously been submitted over the last 15 months which follows in the Appendices A through G. Even when we as a nation reach "herd immunity", COVID-19 will continue to remain a disease of the individual with unvaccinated and immunosuppressed persons in the U.S.A. still at risk. When COVID-19 is initially contracted (and diagnosed) by the unvaccinated individual and not treated with the <u>early</u> administration of <u>Passive Immunization</u> and possibly the concomitant <u>early</u> administration of antivirals, COVID-19 will remain a scourge of the U.S.A. for millennia to come.

As I have done previously over the last fifteen months, I will submit this letter with the accompanying documentation to the FDA; the NIH; the VA (I am a VA federal physician of >23 years); the U.S. Copyright Office of the U.S. Library of Congress; and yourself. In June 2020, in my correspondence with Dr. Fauci, the NIAID of the U.S. National Institutes of Health assigned me a case number (NIAID case # 12276). Thus, by submitting this documentation to Dr. Fauci's office, this information will be entered into NIAID case file #12276. Subsequently, NIAID case #12276 should be available upon request to anyone under the Freedom of Information Act (FIOA). While I will submit this to the U.S. Copyright Office to preserve this for history, I will provide you with this electronically and will mail a hardcopy so that you can reproduce and distribute these documents to whomever you should wish. I waive my right to claim any copyright prohibition to the duplication and reproduction of this material by whomever should wish to do so.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S. Professor, Department of Surgery, Saint Louis University School of Medicine Chief, Unit II General Surgery, Surgical Service (112), John Cochran (St. Louis) VAMC

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27.0 14.0 2021-06-18 Argument for the **EARLY** administration of POLYCLONAL COVID-19 CONVALESCENT PLASMA (CCP) OR POOLED SERA (CCPS)

150 Emerald Green Ct St. Louis, MO. 63141 June 20, 2021 (314) 455-9482

President Joseph Biden 1600 Pennsylvania Avenue The White House Washington, D.C. 202-456-1414

Re: NIAID Case #12276: On March 24, 2020 going forward, the FDA, the NIH, and *The White House* abandoned the USA Public by restricting COVID-19 Convalescent Plasma (CCP) from anyone early-in-the-course of COVID-19 viremia

Dear Mr. President:

Please excuse the forwardness of this letter; but, for the past year, I have written the President of the United States, the Commissioner(s) of the U.S. Food and Drug Administration (FDA), and Dr. Fauci, your present Chief Medical Advisor on the COVID-19 epidemic.¹ As a general surgeon, I never have had the luxury of a patient presenting prior to developing a surgical disease nor treating with a "preventive" operative measure / "preventive" operation prior to the development of a surgical malady. When a patient is referred to me, the patient presents to my office or arrives in the ER having a disease that surgery might treat and a host of surgical therapies that can be employed: open or endoscopic operation or a combination of therapies (e.g., surgical, chemotherapy, radiation, etc.) –But, when no therapy is given, seldom, if ever, has a surgical condition been corrected.

We, as a nation, have essentially abandoned thousands of people who became infected with SARS-CoV-2 virus (COVID-19) during the pandemic--rather than treat **early** (<**72 hours**) with *Passive Immunization* (e.g.: COVID-19 Convalescent Plasma/Serum or Monoclonal antibodies) and an *Antiviral* agent (e.g. Remdesivir) **during the early viremic stage of the disease**. Over the past seven months, **the landmark article** of Romina Libster, M.D., Gonzalo Perez Marc, M.D. *et. al.*: "Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults" was posted first in medR_xiv on November 21, 2020⁵, published in NEJM.org⁶ on January 6, 2021, and republished in *The New England Journal of Medicine* (NEJM)⁷ on February 18, 2021—and essentially ignored. This article was the <u>first</u> and <u>only</u> prospective, randomized, double-blind, placebo-controlled clinical trial in the <u>early administration</u> of High-Titer COVID-19 Convalescent Plasma (CCP) to a <u>select age group</u> (over 75-years-of-age or 65 to 74 with one comorbidity who had contracted COVID-19). Subsequent severe respiratory disease was significantly diminished (P value = 0.03): CCP 13/80 (16.2) and placebo 25/80

(31.2%). Death due to COVID-19 was also diminished by 50%: 2/80 (2.5%) vs. 4/80 (5%) but with the small numbers of the paper did not meet a <0.05% significance. While *The New England Journal of Medicine* published this significant paper as "Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults", the more conclusive, appropriate title in medR_xiv was "Prevention of severe COVID-19 in the elderly by early high-titer plasma" which has had the potential over seven months of redirecting early treatment of COVID-19 to the forefront. Unfortunately, the significance of this article has been minimized and we as a nation have essentially discredited *Passive Immunization* as an empiric early treatment of COVID-19 during the **viremic phase** (<72 hours of diagnosis) in all individuals regardless of age and concomitant illnesses.

While not publicized in a longitudinal fashion by the U.S. Centers for Disease Control and Prevention (CDC), the incidence of increasing mortality (percentage) due to COVID-19 is linearly related to increasing age:

Linear Mortality Incidence by age

Increasing percentage mortality by increasing years

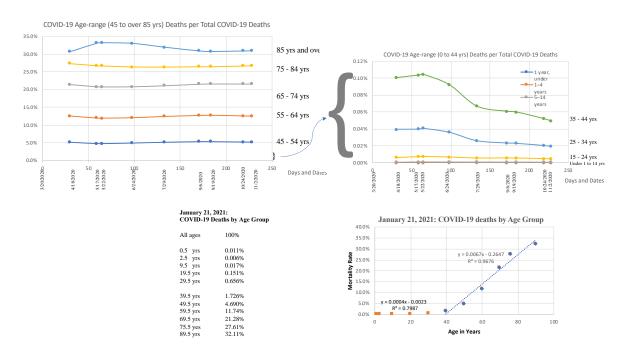
0-40 years of age: y=0.0004x - 0.0023

0.04 % increasing mortality / increasing year

41- 90 years of age: y = 0.0067x - 0.2647

0.67 % increasing mortality/increasing year

Thus, the composite graph is:



As the slope of the graph is so step after age 40 years: 0.67 % increasing mortality / increasing year, any prospective study of mortality due to COVID-19 would require an analysis **stratified by individuals in one age group** like that of Libster, et al. **with treatment early** in the course of

the disease (the viremic phase) to demonstrate significant effect. Unfortunately, the vast majority of the NIH ClinicalTrials.gov were conducted <u>late</u> in the COVID-19 disease in hospitalized patients with severe respiratory and other organ dysfunction during the cytokine cascade and increasing bradykinin levels <u>without stratification by age groups</u>. Essentially, by giving the majority of CCP at the <u>wrong time in the course of the disease of 722,000</u>, U.S. science's *Evidenced-Base Medicine* has discarded the time-validated therapy of *Passive Immunization* in the **early stages of a novel disease** in which early immunologic treatment with antibodies from convalescent patients has been utilized successfully over the last 120 years.

On February 18, 2021, *The New England Journal of Medicine* published 2021 an editorial regarding Libster, *et. al.* by Louis Katz, M.D. entitled: "(A Little) Clarity on Convalescent Plasma for COVID -19" in which Dr. Katz stated that which I have written above but in an obscure fashion, so the reader had little understanding of the significance of Libster, *et. al.* (Please note that Dr. Katz was not fully identified by this paper. Louis Katz, M.D. is "...the former Chief Medical Officer at America's Blood Centers in Washington, DC, an ABC past president, former board member and a past chair of its Scientific, Medical and Technical Committee. His transfusion medicine career has been dominated by attention to transfusion transmitted infections. He has served multiple terms as the chair of the AABB Transfusion Transmitted Diseases committee and served on many AABB committee and working groups. Dr. Katz is on the Editorial Board of the journal Transfusion, has served on the FDA Blood Products Advisory Committee as a member, industry representative and chair, and is a current member of the HHS Advisory Committee on Blood and Tissue Safety and Availability." — Winn KI, Katz L, Goel R: Dr. Louis Katz, Acting Chief Medical Director. ImpactLife (formerly Mississippi Valley Regional Blood Center). https://www.bloodcenter.org/about/news/authors/dr-louis-katz-a4/

The text of this article that follows is verbatim because it explains the mindset of those involved in the FDA's, NIH's, and The White House's convoluted directives and obfuscation in the lack of early treatment during the viremic phase of those infected with COVID-19 with passive immunization (Covid-19 Convalescent Plasma [CCP]) AND THE COVER-UP by US Medicine and the US Government THAT HAS BEEN PERVASIVE OVER THE LAST 15 months. While advocating for the appropriate administration early in the viremic phase of Covid-19 (<72 hours from symptoms/diagnosis) in the outpatient setting and NOT IN THE HOSPITAL SETTING, this New England Journal of Medicine editorial fails to strongly emphasis the definitive utility of PASSIVE IMMUNIZATION and thus has been ignored by the medical community, the US federal government, and the US public-at-large. Even after the FDA quietly removed from all its official documentation on 9/2/2020 the mandate for the strict erroneous CCP administration critera only in severely ill patients initiated by the FDA / vis-à-vis The White House on March 24, 2020 for use only in severely affected patients -- late in the disease administration of CCP (during the cytokine cascade and bradykinin phase which both are dominant in severely hospitalized patients and the only somewhat effective treatment is supportive) continues. The wrong-time administration of CCP became the de facto standard-of-care. The majority of 722,000 doses of CCP given in the U.S.A. over the last 15 months to individuals late in their disease course (and similarly much of the World) was given at the WRONG TIME. — which was such a waste!

And the FDA, the NIH, the VA, *The White House*, the *New England Journal of Medicine*, etc. knew it!

So to Dr. Katz's Editorial:

PASSIVE IMMUNOTHERAPY has been used since the late 19th century, and in 1901, the first Nobel Prize in Physiology or Medicine was awarded for serum therapy for patients with diphtheria. During the 1918 pandemic, serum from convalescent patients was used to treat influenza, with some apparent success.1 Today, the use of immunoglobulins has been established for the prophylaxis and treatment of a variety of infections, including those with respiratory syncytial virus, cytomegalovirus, and hepatitis B or hepatitis A virus. More recently, passive immunotherapy has been evaluated for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and Ebola virus disease. Intravenous human immunoglobulin has revolutionized the management of immunoglobulin deficiency states.

The use of convalescent plasma against SARS coronavirus 2 (SARS-CoV-2) is advocated for the treatment of patients with coronavirus disease 2019 (Covid-19). The experience with influenza A is relevant, and a meta-analysis suggested that **early treatment**, **before critical illness develops**, may be an important **predictor of the efficacy of passive immunotherapy for that pathogen**.1 The authors of that meta-analysis acknowledged the low quality of the available evidence regarding early treatment. Another meta-analysis of studies of convalescent plasma and hyperimmune immunoglobulin in patients with influenza A and SARS suggested a mortality benefit "when convalescent plasma is administered early after symptom onset."2 However, in a randomized, controlled trial, high-titer convalescent plasma from patients who had recovered from H1N1 influenza was ineffective against severe influenza A infection in hospitalized children and adults.3

Initial randomized trials of convalescent plasma in patients with Covid-19 focused on hospitalized patients who were already moderately to severely ill, and these trials provided weak evidence of clinical efficacy. 4-6 Some were underpowered when nonpharmaceutical interventions such as masking and social and physical distancing reduced the incidence of Covid-19 and enrollment was limited. Also, these trials were heterogeneous with respect to the characteristics of the convalescent plasma used (e.g., its antibody content and the stratification of the recipients according to their serologic status). No unexpected safety signals beyond the recognized risks of plasma transfusion (i.e., fluid overload, transfusion-associated acute lung injury, and allergy) have emerged, nor has there been evidence of antibody-dependent enhancement of Covid-19 severity. Accordingly, it is difficult to make actionable conclusions about the clinical value of convalescent plasma.

Observational studies have been more positive than randomized trials; some, but not all, of these studies have suggested modest clinical effects and measurable surrogate virologic outcomes.^{7,8} They have confirmed the safety profile of plasma transfusions but

have some of the same issues as randomized trials, in addition to the potential biases and shortcomings inherent in observational studies.

The Food and Drug Administration (FDA) argued that a "totality of the evidence" suggested that the benefits of convalescent plasma would outweigh its risks, and given the lack of effective treatments, the FDA granted an Emergency Use Authorization (EUA) and provided guidance on the manufacture and use of convalescent plasma in hospitalized patients with signs of progressive infection. By contrast, a National Institutes of Health guidelines panel stated that "the data are insufficient to recommend for or against" the use of convalescent plasma. The Infectious Diseases Society of America and the AABB (formerly known as the American Association of Blood Banks) recommend that the use of convalescent plasma be limited to clinical trials, that critically ill patients and those in the intensive care unit (ICU) are unlikely to benefit from transfusions of convalescent plasma, and that convalescent plasma should be used as early as possible in the course of infection (preferably within 3 days after diagnosis) in order to achieve the best outcomes.9

Considering the number of SARS-CoV-2 infections, the paucity of treatment options, and the enthusiasm for and controversy about convalescent plasma, a high-quality, multicenter, randomized, controlled trial is most welcome. Libster and colleagues now report in the Journal¹⁰ the results of a well-executed trial of early convalescent plasma in older adult patients in whom symptomatic SARS-CoV-2 infection was diagnosed with the use of a polymerase-chain-reaction assay. In this double-blind trial, 250 ml of convalescent plasma with an IgG titer greater than 1:1000 against SARS-CoV-2 spike (S) protein was compared with saline placebo in patients who were 65 to 74 years of age and had prespecified coexisting conditions and in patients who were 75 years of age or older with or without coexisting conditions.

The patients received convalescent plasma or placebo less than 72 hours after symptom onset. In the intention-to-treat population, a primary end-point event (progression to predefined severe disease during follow-up) occurred in 16% (13 of 80 patients) and 31% (25 of 80 patients) of the well-matched convalescent plasma and placebo groups, respectively. A dose-dependent effect relative to the antibody titers after infusion was observed, and this effect was larger after the exclusion of 6 patients who had a primary end-point event before infusion. The benefits of convalescent plasma with respect to the secondary end points were consistent with those associated with the primary end point. No serious adverse events were observed. The authors conclude that "early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19." Even before the current trial, the EUA emphasized the potential advantages of early therapy with high-titer convalescent plasma. Unfortunately, a direct comparison of antibody levels in the current trial with assays specified in the FDA EUA is not available. Antibody titers in the recipients at enrollment were not provided, so no comment can be made about the usefulness of seroreactivity in patients as a criterion for convalescent plasma use.

At this time, <u>convalescent plasma</u> should be reserved for patients in whom the duration, severity, and risk of progression of illness are similar to those in the patients in this trial. Younger high-risk patients (and certain immunodeficient patients) with these disease characteristics should be considered as well.

The supply of convalescent plasma has been tenuous during the marked increase in Covid-19 cases during the fall in the United States, although recent collections have improved. From September 28 through December 27, 2020, distributions of new and stockpiled units of convalescent plasma to hospitals in the United States exceeded collections by 7785 units (Block W: personal communication). If collections are restricted to the high-antibody titers and patient indications described in the article by Libster et al., the supply of convalescent plasma will be stressed. At my center, high-titer collections (as defined by the FDA) account for only 19.5% of seroreactive convalescent plasma donations. Shifting the pool of potential recipients away from those included in the EUA to the many infected outpatients whose risk of hospitalization and eventual need for advanced care cannot be precisely estimated should lead to the extension of convalescent plasma transfusions to prehospital venues (although this is not yet permitted in the EUA).

Uncontrolled compassionate use of convalescent plasma in patients other than those with an early infection that is likely to progress to more severe illness should be discouraged, even though clinicians recognize how difficult it can be to "just stand there" at the bedside of a patient in the ICU. Constraints on therapies for Covid-19 that are effective for limited patient populations are a powerful argument for continued consistent adherence to recommended nonpharmaceutical interventions and the rapid deployment and uptake of effective vaccines.

In an obfuscating way, Dr. Katz is stating that when high-dose COVID-19 Convalescent Plasma is given early (<72 from time of onset or diagnosis) and is compared with placebo in agematched patients ~70 years of age, progression to severe COVID-19 disease (e.g. pneumonitis, blood clots, etc.) is 16% versus 31%, respectively. <u>Uncontrolled compassionate use of convalescent plasma in patients other than those with an early infection that is likely to progress to more severe illness is exactly what the USA has WRONGLY DONE for the last 15 months.</u>

The most disingenuous understatement in Dr. Katz's article was the assertion that: "Even before the current trial, the EUA emphasized the potential advantages of early therapy with high-titer convalescent plasma." In fact, all EUAs regarding COVID-19 Convalescent Plasma (CCP) from the initial one on August 23, 2020 have always advised that it must be given early in the course of the disease and in high dose. Unfortunately, when CCP was first introduced to the American public on March 24, 2020, the stipulation was that it be given to patients that only met a late-in-the-disease severity eligibility criteria:

· Eligible patients for use under expanded access provisions:

- Must have laboratory confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale...

2/3

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

- multiple organ dysfunction or failure
- Must provide informed consent

¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

In the second opened circle bullet of the aforementioned quote: "...Eligible patients for use under expanded access provision!"... of the FDA directive of March 24, 2020, the reference 1 (only reference in the entire paper listed) was the only justification of the directive for Investigational COVID-19 Convalescent Plasma – Emergency INDs, March 24, 2020 (https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20_%20FDA.pdf] regarding the Eligibility Criteria. This justification was a misread and misinterpretion from the referenced: Wu Z, McGoogan JM: Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention in which the article never speaks of treatment with CCP. This reference was an epidemiology report in which it was stated that 14% of the 72,314 cases had severe COVID-19 disease demonstrated the components of the "Eligibility Criteria" BUT the FDA had NO justification upon which to base the eligibility criteria for administering CCP to only those people. The actual quote from Wu and McGoogan is as follows:

Most case patients were 30 to 79 years of age (87%), 1% were aged 9 years or younger, 1% were aged 10 to 19 years, and 3% were age 80 years or older. Most cases were diagnosed in Hubei Province (75%) and most reported Wuhan-related exposures (86%; ie, Wuhan resident or visitor or close contact with Wuhan resident or visitor). Most cases were classified as mild (81%; ie, nonpneumonia and mild pneumonia). However, 14% were severe (ie, dyspnea, respiratory frequency \geq 30/min, blood oxygen saturation \leq 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio \leq 300, and/or lung infiltrates \geq 50% within 24 to 48 hours), and 5% were critical (ie, respiratory failure, septic shock, and/or multiple organ dysfunction or failure) (Box).

On March 26, 2020, the *British Medical Journal* reported the Eligibility Criteria *verbatim* and yet the three references quoted by this *BMJ* article reference electronically three references that are now linked in an *ex post facto* fashion to the URL of the FDA published directive of February 11, 2021. *In short, the BMJ, the NBC News, and the National Public Radio (NPR)* references now point to the URL of an FDA directive dated by the Internet Archive (the Wayback Machine) to now be 10 months after the FDA issued the direction on March 24, 2020. There are only two feasible explanations for this occurrence, the BMJ, NBC News, and NPR are clairvoyant <u>OR</u> the FDA has destroyed electronically U.S. government documentation (which is a federal violation of the law by the FDA)! Employing the Internet Archive (the Wayback Machine), the original website for the Mayo Clinic Expanded Access program (in conjunction with the FDA) of April 4, 2020

[https://web.archive.org/web/20200404010134/https://www.uscovidplasma.org/], reiterates the FDA Eligibility Criteria of the FDA directive of March 24, 2020 thus confirming the previous actual existence of the FDA directive on March 24, 2020 even though the official FDA URL is now pointing to February 11, 2021. (I would allege the electronic destruction of this FDA documentation is a criminal offense.)

From April 8, 2020 to September 1, 2020, the late-in-the-disease Eligibility Criteria existed in *U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma* as is documented in the digital photograph of the Internet Archive (the Wayback Machine) on September 1, 2020:

https://web.archive.org/web/20200901081726/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma#Patient%20Eligibility which was the version issued on August 23, 2020 by the FDA which is the same day the first EUA of for COVID-19 Convalescent Plasma was issued by the FDA Chief Scientist, Rear Admiral Denise M. Hinton and proclaimed in *The White House* press conference on August 23, 2020 by President Trump.

August 23, 2020: U.S. FDA Chief Scientist, Rear Admiral Denise M. Hinton: "Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of disease."

September 2, 2020: The FDA removed the late-in-the-disease Eligibility Criteria from the *U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma* as is documented in the digital photograph of the Internet Archive (the Wayback Machine) on September 2, 2020. The FDA remove the late-in-the-disease Eligibility Criteria on September 2, 2020 to the present day but didn't tell anyone as far as I can find: https://web.archive.org/web/20201115054330/https://www.fda.gov/vaccines-blood-

biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

Thus, from August 23, 2020 until September 2, 2020, the EUA proclaimed by President Trump was contradicted by that which was in *U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma*. What is more, <u>de facto</u> most physicians, hospitals, blood banks, politicians, the American public, etc. still believe that administration of CCP per the FDA's late-in-the-disease Eligibility Criteria is still the <u>Standard of Care! This is a travesty, and *de facto* patient abandonment promoted by the FDAs obfuscation and <u>failure to notify the World that they had rescinded the Late-in-the disease Eligibility Criteria on September 2, 2020.</u></u>

November 30, 2020: U.S. FDA Chief Scientist, Rear Admiral Denise M. Hinton: FDA Chief Scientist, Rear Admiral Denise M. Hinton: "Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of disease."

February 2, 2021: _____, OBRR/DBCD/CRS, U.S. FDA: Clinical Memorandum:

- 1) Page 1-2: "...It is reasonable to conclude that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA. Current data suggest the largest clinical benefit is associated with high-titer units of CCP administered early in the course of disease. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient population for its use."
- 2) Page 6: "...Hamster studies found that postinfection sera fro hamsters previously infected with the virus administered to other hamsters following infection with SARS-CoV-2 was able to decrease viral loads[35]. A separate study found immunoprophylaxis with early convalescent serum achieved a significant decrease in lung viral load but not in lung pathology[36]. In mouse studies, administration of 150 μL of human CCP one day prior to SARS-CoV-2 infection prevented weight loss and lung tissue histological changes, and accelerated the rate of virus clearance[37]. More rapid clearance of SARS-CoV-2 infections was not observed after treatment with pooled plasma from SARS-CoV-1 survivors or MERS survivors."
- 3) Page 8: "Using a propensity score matching algorithm, Salazar et al[21] found 28-day mortality was 3.7% in 136 CCP transfused subjects with severe COVID-19 versus 7.6% in 543 non-transfused controls (p=0.13). In those transfused within 72 hours of admission and with high-titer units, there was a significant difference in 28-day mortality (1.2% in CCP vs 7.0% in control, p = 0.047). The authors concluded that transfusion of high anti-RBD IgG titer COVID-19 CCP early in hospitalization reduces mortality."
- 4) Page 11: "Current evidence suggests that benefit is most likely in patients treated early in the course of the disease (e.g., prior to intubation). In addition, as outlined in the data reviewed above from different studies, there is a potential benefit of CCP in intubated and non-intubated patients. Considering the absence of a control population in the EAP and that data from randomized trials remain limited, the lack of benefit observed in intubated patients in this study is currently insufficient to exclude potential benefit in this population. Therefore, bearing in mind the safety profile observed to date, inclusion of intubated and non-intubated patients under the EUA appears appropriate at this time."

5) Page 13: "Current evidence suggests clinical benefit is most likely in patients treated early in the course of the disease (e.g., prior to intubation) and with the use of CCP with higher antibody levels or neutralization activity."

THUS, Confirmed by the Chief Scientist of the U.S. Food & Drug Administration, COVID-19 CONVALESCENT PLASMA WHEN GIVEN EARLY IN THE VIREMIC PHASE OF COVID-19 (<72 HOURS after diagnosis) HAS A DECREASE / OBSERVED REDUCTION IN PROGRESSION TO THE LATER MULTISYSTEM-ORGAN-FAILURE (MSOF) PHASE OF COVID-19 and MORTALITY INVOLVING: (1) THE CYTOKIN STORM AND (2) THE ACCUMULATION OF DETRIMENTAL LEVELS OF BRADYKININ.

COVID-19 Convalescent Plasma and monoclonal antibodies and cocktails, which your administration has now purchased, are **literally the same thing**—only CCP is <u>poly</u>clonal but much more available. **Some form of** *Passive Immunization* **should be administered early** (**within 72 hours after diagnosis**) and should be made available to <u>ALL</u> the people of the United States (and the World) who contract COVID-19. It was no fluke that President Trump, former Governor Christie, former Mayor Rudolph Giuliani, and former HUD Secretary Ben Carson, M.D. did well after treatment with *Passive Immunization* and the antiviral Remdesiver – that should be the EARLY **standard-of-medical-care** when any individual contracts COVID-19.

As I have done previously, I will submit this letter with the accompanying documentation to the FDA; the NIH; the VA (I am a VA federal physician of >23 years); the U.S. Copyright Office of the U.S. Library of Congress; and yourself. In June 2020, in my correspondence with Dr. Fauci, the NIAID of the U.S. National Institutes of Health assigned me a case number (NIAID case # 12276). Thus, by submitting this documentation to Dr. Fauci's office, NIAID case #12276 should be available upon request to anyone under the Freedom of Information Act (FIOA). While I will submit this to the U.S. Copyright Office to preserve this for history, I will provide you with multiple CD-burned copies so that you can reproduce and distribute these documents to whomever you should wish might review, copy, or post this informational documentation.

Respectfully yours,

Charles H. Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine Chief, Unit II General Surgery, Surgical Service (112), John Cochran (St. Louis) VAMC As health care workers, medical scientists, and, in increasing numbers, the general population have been vaccinated, those vaccinated have returned to the onlooker position of the crashing plane rather than the at-risk passengers on the crashing plane. This concept is consistent with what occurred over an eight-year period involving the failure of the VHA's PSRS⁴:

Using the 26-year-old Aviation Safety Reporting System (ASRS), the National Aeronautics and Space Administration (NASA)-directed reporting system for the Federal Aviation Administration (FAA) as the "gold standard," such methodologies have operated on the assumption that if a system claims to be anonymous, non-discoverable, nonpunitive, and the best interests of the patient, health care personnel will willing report. Unfortunately, As Dr James Bagian, former astronaut and now director of the National Center for Patient Safety, Veterans Health Administration (VHA), eloquently stated recently before the joint annual meeting of the Association of Program Directors in Surgery and the Association for Surgical Education, the ASRS works not only because it is voluntary, nondiscoverable, anonymous, and nonpunitive, but also because the pilot is always the first to the crash site. In any medical error reporting system, it is usually the individual patient who is physically at risk, not the medical personnel. Yet our nation's hospitals, medical systems, and governmental organizations have invested much time, money, and effort in establishing such error-reporting systems modeled after the ASRS in which the primary incentive to report—preservation of one's own life (as opposed to one's own livelihood) is missing.

While this quote may seem discordant with the present COVID-19 Pandemic, the incentive of medical personnel (especially as it has been ignored by U.S. Medicine, the FDA, the NIH, and The New England Journal of Medicine (NEJM), etc. for the last year) to treat within 72 hours of contraction (positivity with early or no symptoms) of COVID-19 to all affected individuals with Passive Immunization and Antivirals has been missing in the last 15 months and becomes diminished as "herd immunity" is approached. Over the past seven months, the landmark article of Romina Libster, M.D., Gonzalo Perez Marc, M.D. et. al. was posted first in medRxiv on November 21, 2020⁵, published⁶ in NEJM.org on January 6, 2021, and republished⁷ in *The* New England Journal of Medicine (NEJM) on February 18, 2021 reported the first prospective, randomized, double-blind, placebo-controlled early administration of High-Titer COVID-19 Convalescent Plasma (CCP) to a select age group (over 75-years-of-age or 65 to 74 with one comorbidity) who had contracted COVID-19 and subsequently severe respiratory disease was significantly diminished (P value = 0.03): CCP 13/80 (16.2) and placebo 25/80 (31.2%). Death due to COVID-19 was also diminished: 2/80 (2.5%) vs. 4/80 (5%) but with the small numbers did not meet a <0.05% significance. While The New England Journal of Medicine published this significant paper as "Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults", the more conclusive, appropriate title in medR_xiv was "Prevention of severe COVID-19 in the elderly by early high-titer plasma" which had the potential of redirecting early treatment of COVID-19 to the forefront.

Beginning in March of 2020, the FDA, the NIH, the CDC, *The White* House, and Organized Medicine misdirected the **appropriate early treatment** (<72 hours from diagnosis) of all

COVID-19 positive individuals with CCP (**Passive Immunization**) and later in regards to the antiviral remdesivir). by:

- 1) misinterpreting definitions, e.g.:
- A] Denying the biosimilarity of COVID-19 Convalescent Plasma with rabies vaccine, gamma globulin, hyperimmune tetanus passive immunization, RhoGam, etc. by declaring COVID-19 Convalescent Plasma as an Investigational New Biologic instead of that which it is as a biosimilar biologic passive immunization agent (even though Dr. Fauci was the senior author of an NEJM review article on Passive Immunization in the treatment of emerging viral illnesses);
- B] Befuddling the American people and their healthcare providers by confusing the absolute distinctions between Phase I (safety) trials and Phase II/III (efficacy) trials thus *de facto* denying all Americans' begging for their inalienable rights to health (*vis-à-vis* the Pursuit of Happiness) by the NIH and FDA misconstruing and thus evading the intent and application of PL-115-176, the 2018 Right to Try Law throughout the last 15 months;
- C] Providing COVID-19 Convalescent Plasma initially for five months by an FDA approved Expanded Access (really compassionate use) protocol thus disqualifying all data generated as not officially and/or ethically available for any conclusive medical research trials;
 - D] As of August 23, 2020, providing COVID-19 Convalescent Plasma
- 2) electronic overwriting of policies and directives thus obfuscating and misdirectly; 3) changing URLs so information was essentially non-discoverable; and 4) removing announcements/policies from URLs which was destruction of documentation. Combinations of applications above have lead to early implementation of Passive Immunization techniques and antiviral drugs.

An algorithm of isolation, prevention, and treatment is essential in addressing any novel virus like SARS-CoV-2. (Chart I)

References:

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28.0 15.0 2021-02-27 A Plea for EARLY (<72 hrs) Passive Immunization and an Antiviral to EVERY man, woman, and child infected with COVID-19

Dear Mr. President:

Over the last 11 months I've attempted to communicate with the White House, the FDA, the NIH, the NEJM, and anyone else who might listen regarding **Passive Immunization** in the **early** treatment of COVID-19. As a federal physician since 1982 (officially for >23 years and in advocacy for Veterans for the proscription of "Ghost Surgery" in the VA¹⁻⁹, I have written and documented over the last year in the U.S. Copyright Office of the Library of Congress my correspondence of advocacy for the utilization of Passive Immunization, which is a treatment, not the prevention, of COVID-19.¹⁰⁻¹² As a general surgeon since the 1980s, I realize the truism that surgical patients that develop a disease will not/cannot be treated with prevention. Patients always present to me with a condition and/or disease. In the middle of an operation, I cannot leave never-coming-back to the table thus abandoning the patient. In the mindset of always Primum non Nocere, I must do to the best of my technical knowledge, ability, and resolve that which will promote healing, possibly a cure, and the best chance of survival for each and every individual patient. In March 2020, we collectively forgot as a country with silent acquiescence of the Medical Profession that withholding SAFE treatment therapy was not consistent with our oaths of *Primum non Nocere*. The treatment of a disease is just that—TREATMENT—not prevention. Those in the know on March 24, 2020, knew that convalescent plasma could be effective in the treatment of COVID-19. (Appendix A) Unfortunately, due initially in March 2020 to the small numbers of COVID-19 convalescent (recovered at least 14 days) patients, passive immunization in the form of Convalescent Plasma (polyclonal antibody therapy) was in short supply in the USA (China had offered 90 tons of surplus to Italy in that month) and monoclonal antibody therapy was non-existent and on the drawing boards. Thus, the FDA develop guidelines for COVID-19 Convalescent Plasma to be given only at the 11th hour—atdeaths-door so to speak which is the WRONG TIME to administer **Passive Immunization**.

We disingenuously minimized the collective knowledge of the last 120 years that **Passive Immunization** to-be-maximally effective needs to be given immediately (<72 hours) upon contraction, identification (testing), or development of the early signs of disease or condition TO **ALL** whether it be rabies, unvaccinated tetanus victims, SARS-CoV-1, post-partum Rh negative mothers, ebola, MERS, or SARS-CoV-2 (COVID-19). This WRONG administration time was quietly removed for both Remdesivir (August 28, 2020) and Convalescent Plasma (September 2, 2020) without significant public notification to the American public, hospitals, or practicing physicians and continued application in many hospitals (including the VA) for months later. There is an elaborate timeline documented in my correspondence with Washington over the last 10 months that one can see of the misdirections that were taken if one knows how to use the Internet Archive--The Wayback Machine (I would suggest you ask your grandchildren to research this for you rather than federal officials with their self-interest agendas on how to use the Internet Archive out of San Francisco). Using the Wayback Machine with the latest URLs of the FDA, NIH, CDC, and PHS announcements, the EUAs and FDA Instructions to Industry regarding Remdesivir, COVID-19 Convalescent Plasma, Monoclonal Antibodies, etc. will provide you with earlier versions that have been overwritten if the federal agencies have not changed the URLs which I would allege that such URL changes are tantamount to destruction of the chronology of legal documentation, obfuscation, and preventing appropriate legal discovery (a federal crime). Striving for medical absolute "political correctness" throughout the last 11 months, we have wandered our way through the COVID-19 forest looking at each and every individual tree disjointedly and never applying fundamental Medical history, knowledge, and common sense at the right time. We failed to listen to such physicians as Drs. Deborah Birx, Jay Epstein, Arturo Casadevall, and Michael Joyner. We failed to recognize that there are three independent variables affecting the treatment of COVID-19:

- 1.) the pathophysiology of the <u>viremia</u> early in the course of SARS-CoV-2 infection,
- 2.) age of the patient (See Graph I), and
- 3.) the need for early treatment time during initial viremia.

Not addressing this disease by not taking into account all three of equal importance independent variables is doomed to failure.

The first commandment states: *I am the Lord your God*, *you shall not bring other gods before me*. We have had numerous false gods that have played out in this tragedy: greed, ignorance, meanness, power, disregard for the law, and, most of all, diminishment of individual human value and equal individual worth of each and every person of the U.S.A.

We have changed or modified definitions so as to diminish applying a simple concept of treatment of a disease: early-phase COVID-19 asymptomatic or minimally-symptomatic viremia vs. late-phase markedly symptomatic pneumonic Severe Acute Respiratory Syndrome (SARS); treatment vs prevention (vaccination); active vs. passive immunization; Phase I (safety) vs Phase II/III (efficacy) clinical trials thus negating the Right to Try Act, PL 115-176; advocacy for placebo controls in the face of <u>no other</u> treatment is unethical; expanded access (compassionate use) vs medical clinical trial data; and withholding-of-care in the name of the "diety" of absolute Evidence-based Medicine.

We have covered-up ongoing information by overwriting FDA, CDC, etc. URLs so as to hide ongoing collective data, mortality trends by age, and all prior missteps. We have failed to be accountable: e.g.: the little box and arrow which is a hyperlink to all executive branch federal agencies as a disclaimer of a non-governmental site and thus no federal responsibility/ accountability (e.g. www.uscovidplasma.org); changing URLs for the same topic making chronologic review difficult (if not impossible) to discover; mailing official federal governmental information and responses by federal government agencies by Federal Express or UPS Express instead of USPS Express Mail (Appendix II) so as to avoid the oversight of the U.S. Postal Inspectors; Presidential distraction by misinformation regarding intravenous disinfectants (IV poisons) vs that which had been discussed on April 24, 2020 regarding COVID-19 Convalescent Plasma; etc.

For most of the last four years we, as a nation, have experienced unfortunately the misconception that to say one is "sorry" is a sign of weakness (not strength--when it is appropriate) and that to ask forgiveness should be always avoided. After Watergate in 1982, the US Supreme Court confirmed in a 5 to 4 decision in *Nixon v Fitzgerald* that the President of the United States of America has absolute immunity from all civil litigation for the rest of his life admonishing in the

opinion of the Court that the Congress and the free press will temporize Presidential absolute immunity—in short, establishing unwittingly the possibility of that which our founders fought against at all cost—the divine right of kings. Your predecessor utilized this Supreme Court opinion incessantly becoming a master of inuendo employing it in ad hominum attacks against his political opponents and became a judge, jury, and figuratively executioner--denouncing the free press, the downtrodden, immigrants, Democrats, and POWs and fallen military as losers. We, as a country at the beginning of the USA COVID-19 epidemic **Screwed Up!** For our very survival in the future, we need to listen, consider, and compromise, correct what we can, and move on.

Mr. President, I plead with you to consider mandating as a **standard-of-care** for all who turn positive in the **TREATMENT** of COVID-19 ASAP (hopefully <72 – 96 hours) of:

- 1) **Passive Immunization** (polyclonal COVID-19 convalescent plasma or monoclonal antibodies),
- 2) an antiviral (e.g.: Remdesivir, (Velkury), NDA 214787, and,
- 3) if the patient develops pneumonitis or SARS symptomatology, dexamethasone.

Institute a national plasma blood drive through the Association of American Blood Banks and the American Red Cross being completely and responsibly overseen by the FDA which is the FDA's statutory mandate. Organize (possibly through the VA hospitals and CBOCs) a federal administration methodology for provision of the above to all newly infected COVID-19 victims, Veterans and non-Veterans alike. As the COVID-19 variants emerge, Convalescent **Sera** should be developed (pooled Convalescent Plasma) for administration in the early treatment (in the viremic stage) of all newly positive COVID-19 victims so as to treat all emerging variants in the coming future.

Mr. President, most of all for the ongoing fight and treatment of and individual survival from COVID-19 and its variants, you should probably meet (either in one room or by computerized group meeting methodology-- <u>but at the same time</u> – and listen to their discussion about Passive and Active Immunization, etc.) with Deborah Birx, M.D., Jay S. Epstein, M.D., Arturo Casadevall, M.D., M.S., Ph.D., Michael Joyner, M.D., Anthony Fauci, M.D., Francis Collins, M.D., Ph.D., Janet Woodcock, M.D, Richard Stone, M.D., Monty Wilkinson, J.D., and Jeffrey A. Rosen, J.D. I plead with you to consider this submission for the survival of our nation.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.
Professor, Department of Surgery, Saint Louis University School of Medicine
Chief, General Surgery II (SLU division), Surgical Service (112), St. Louis (John Cochran)
VAMC

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P.S. I will submit a composite of this to you through the USPS priority mail (the Brentwood Post Office will not accept Express Mail for The White House and submit this as emails, etc, to the physicians mentioned above in the FDA, NIH, VA, Mayo Clinic, Johns Hopkins. Hopefully, Dr. Fauci, as your top Medical Advisor on COVID-19, will provide this to you as soon as he can. Thank you for this consideration, Charles H. Andrus, M.D.

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BOOK 1, Volume 2:

Dear Mr. President: COVID-19 and Where We Went Wrong

Charles H. Andrus, M.D., F.A.C.S. February 1, 2023

29.0 Timeline Bibliography

30.0 10 2022-05-30 Bibliographic Timeline References

31.0 20 2022-05-30 annotated Timeline References
[This is extensive annotation of the greater than
1100 references in the listing above]

For educational purposes of the People of the United States of America

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such an important article that it has been copied and pasted to follow in its entirety. This is the NIH's justification of merging Phase I (safety) trials with Phase II (efficacy) trials so as to circumvent completely ever applying PL-115-176: The Right to Try Law with regards to COVID-19 Convalescent Plasma but also any future investigational drug or biologic <u>ad infinatum</u>. This obfuscation by the NIH is tantamount to justifying repeated violations of PL-115-176 and is ethically shameful!].

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 Please note that this fact sheet regarding Regeneron's monoclonal antibody cocktail exists to this day. The criteria for administration of casirivimab and imdevimab in the Black Box is stated for only in patients who have mild to moderate symptoms outside of hospital "...at high risk for progressing to severe COVID-19 and/or hospitalization..." This is arbitrarily based on a physician's ability to predict the future outcome of the individual patient regarding administration to or withholding from early in the disease process of the individual patient and has led to withholding of casirivimab and imdevimab and thus defacto rationing of a safe treatment that should be available to all people who become COVID-19 positive within 72 hours of positivity.
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- 738) 2021-02-01 Andrus CH:

Dear Dr. Birx:

On March 24, 2020, while there was much discussion and debate about COVID-19 convalescent plasma and the possible development of monoclonal antibodies against COVID-19, U.S. Medicine and the Government failed to explain to the American public the differences and individual utilities of *Active Immunization* (vaccines to stimulate patient antibody production) and *Passive Immunization* (provision of convalescent plasmas, convalescence sera, and immunoglobins from other species providing already formed antibodies (IgM, IgG, and IgA) against the virus in COVID-19 immunologically naïve patients immediately within 72 hours of diagnosis (testing positive).

Etc—See attached letter to Dr. Birx.

739) 2021-02-02 U.S. Food & Drug Administration: CLINICAL MEMORANDUM, EUA 26382, COVID-19 Convalescent Plasma (CCP). NONE OF THE VERSIONS OF THESE MEMOs are dated and thus dating was obtained from the digital captures using the Internet Archive (WayBack Machine). The URL of this Memorandaum is: https://www.fda.gov/media/141480/download

EXECUTIVE SUMMARY COVID-19 Convalescent Plasma (CCP), an unapproved biological product, is proposed for use under an Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act),(21 USC 360bbb-3) as a passive immune therapy for the treatment of hospitalized patients with COVID-19, a serious or life-threatening disease. There currently is no adequate, approved, and available alternative to CCP for treating COVID-19. The sponsor has pointed to four lines of evidence to support that CCP may be effective in the treatment of hospitalized patients with COVID-19: 1) History of convalescent plasma for respiratory coronaviruses; 2) Evidence of preclinical safety and efficacy in animal models; 3) Published studies of the safety and efficacy of CCP; and 4) Data on safety and efficacy from the National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.

- 740) 2021-02-04 Hinton DM: U.S. Food and Drug Administration Letter to Nikki Bratcher-Bowman, Acting Assistant Secretary for Preparedness and Response, EUA-update regarding COVID-19 Convalescent plasma. February 4, 2021. (Please note that the position of Assistant Secretary of Preparedness and Response changed from February 2, 2021 (48 hours previous) from Robert Kadlec, M.D. who had been appointed by President Trump to an Acting Assistant Secretary for Preparedness and Response under the Biden Administration: Nikki Bratcher-Bowman.)

 https://web.archive.org/web/20210218201225/https://www.fda.gov/media/141477/download
- 741) 2021-02-04 U.S. Food & Drug Administration: FDA in Brief: FDA Updates Emergency Use Authorization for COVID-19 Convalescent Plasma to Reflect New Data, February 4, 2021. This is deliberate legal obfuscation on the part of the FDA by stating that it was

Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Prevention: Active Immunization: Vaccines

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limiting authorization-- de facto, the FDA was really expanding authorization by appropriately limiting the EUA for COVID-19 Convalescent Plasma to "early in the disease course" which was contrary to FDA directives from March 24, 2020 to September 2, 2020 when the criteria was that CCP could only be given to severe patients late in the disease course. The provision of CCP late in the disease course was de facto perpetuated by the fact that the FDA had unobtrusively removed the strict severity of illness criteria late in the disease course from all FDA documentation by overwriting on September 2, 2020 and going forward on all subsequent documentation and not announcing it officially to the U.S. Medical and Research Community, probably the rest of the Federal Government, and most definitely not to the American people. The "high dose" vs "low dose" concern is a secondary issue—that was used as a distraction by the FDA--as with monoclonal antibodies/antibody cocktails, COVID-19 Convalescent Plasma and monoclonal antibodies are all Passive Immunization and are therapeutically identical if given **EARLY IN THE COURSE OF THE DISEASE**. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-updates-emergency-useauthorization-covid-19-convalescent-plasma-reflect-new-data

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Authorized Use

The FDA has authorized the emergency use of PAXLOVID, an investigational medicine, for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with a positive test for the virus that causes COVID-19, and

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who are a at high risk for progression to severe COVID-19, including hospitalization or death, under an EUA.

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8) 1865-03-04 Lincoln A: President Abraham Lincoln's Second Inaugural Address. OurDocuments https://www.ourdocuments.gov/doc.php?flash=false&doc=38

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan—to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

- 9) 1865 Carroll, Lewis, (Charles Lutwidge Dogson) *Alice's Adventures in Wonderland*. London: MacMillan and Co., 1866. <a href="https://www.etsy.com/listing/1018008039/dodgson-charles-lutwidge-lewis-carroll?gpla=1&gao=1&&utm_source=google&utm_medium=cpc&utm_campaign=shopping_us_a-books_movies_and_music-books-childrens_books&utm_custom1=_k_EAIaIQobChMIwKjN_s2T9QIVAHNvBB1qWwZME_AQYAyABEgJqavD_BwE_k_&utm_content=go_12573073822_126376635984_507798475_344_aud-1185363470307:pla-352609785060_c_1018008039_468327882&utm_custom2=12573073822&gclid=EAIaIQobChMIwKjN_s2T9QIVAHNvBB1qWwZMEAQYAyABEgJqavD_BwE_
- 10) 1885 Twain M: First edition of the Adventures of Huckleberry Finn with an E.W. Kemble Illustration Laid In. New York: Charles L Webster and Company, 1885. (an early example of Twain's book.) https://www.raptisrarebooks.com/product/adventures-of-huckleberry-finn-mark-twain-first-edition-1885/
- 11) 1885-07-06 CDC: Historical perspectives a centennial celebration: Pasteur and the modern era of immunization. MMWR 9185 Jul 05; 34(26): 389-90. https://www.cdc.gov/mmwr/preview/mmwrhtml/00000572.htm
- 12) 1873 Saxe JG: *The Blind Men and the Elephant*. This was a retelling by the American poet John Godrey Saxe of an Indian parable which epitomizes how individuals over the last several years with personal vested interests and self-promotion (e.g.: conflicts of interest to advance financial advancement, preserve the *status quo* with regards to research grants, misdirection of informed consents and continue coercion in research trials, etc.) have skewed the addressing of the COVID-19 pandemic for personal advancement. https://www.commonlit.org/en/texts/the-blind-men-and-the-elephant

It was six men of Indostan To learning much inclined, Who went to see the Elephant Though all of them blind, That each by observation Might satisfy his mind.

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"God bless me, but the Elephant Is very like a wall!"

The Second, feeling the tusk Cried, "Ho! What have we here So very round and smooth and sharp? To me 'tis very clear This wonder of an Elephant Is very like a spear!"

The Third approached the animal And, happening to take The squirming trunk within his hands, Thus boldly up he spake: "I see," quoth he, "The Elephant Is very like a snake!"

The Fourth reached out an eager hand, And felt about the knee: "What most the wondrous beast is like Is very plain," quoth he; "Tis clear enough the Elephant Is very like a tree!"

The Fifth, who chanced to touch the ear, Said, "Even the blindest man
Can tell what this resembles most:
Deny the fact who can:
This marvel of an elephant
Is very like a fan!"

The Sixth no sooner had begun About the beast to grope Then, seizing on the swinging tail That fell within his scope, "I see," quoth he, "the Elephant Is very like a rope!"

And so these men of Indostan Disputed loud and long, Each in his own opinion Exceeding stiff and strong.

Though each was partly in right, They all were in the wrong!

13) 1887 Acton: Lord Acton writes to Bishop Creighton that the same moral standards should be applied to all men, political and religious leaders included, especially since "Power tends to corrupt and absolute power corrupts absolutely." OLL https://oll.libertyfund.org/quote/lord-acton-writes-to-bishop-creighton-that-the-same-moral-standards-should-be-applied-to-all-

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- men-political-and-religious-leaders-included-especially-since-power-tends-to-corrupt-and-absolute-power-corrupts-absolutely-1887
- 14) 1905 Santayana G: "Those who cannot remember the past are condemned to repeat it", *The Life of Reason*, 1905. From the series Great Ideas of Western Man. SAAM, Smithsonian American Art Museum. https://americanart.si.edu/artwork/those-who-cannot-remember-past-are-condemned-repeat-it-george-santayana-life-reason-1905
- 15) 1905 Robert E. Gross, M.D., born: Clatworthy HW: Robert E. Gross. https://pubmed.ncbi.nlm.nih.gov/3095885/ and https://fa.hms.harvard.edu/files/memorialminute gross robert e.pdf
- **16)** 1913 ACS: History of the American College of Surgeons. https://www.facs.org/about-acs/archives/acshistory
- 17) 1918-1919 CDC: History of the American College of Surgeons. https://www.facs.org/about-acs/acs-history/
- 18) 1926 de Kruif P: *Microbe Hunters*. New York: Harcourt, Brace, and Co., 1926. (New York: Paul de Kruif, Harcourt, Brace, Co., copyright renewed 1954). https://laurieximenez.files.wordpress.com/2016/03/2-microbe-hunters-paul-de-kruif.pdf
- 19) 1927-03-19 Peabody FW: The Care of the Patient. J Am Med Association. 1927 March 19; 88 (12): 877-882. (Presented at Boston Hospital, October 21, 1925). https://depts.washington.edu/medhmc/wordpress/wp-content/uploads/Peabody.html
- **20)** 1933-03-04: Roosevelt FD: Inaugural Address of the President, Washington, D.C., March 4, 1933. https://www.archives.gov/files/education/lessons/fdr-inaugural/images/address-1.gif
 - ...So, first of all, let me assert my firm belief that the only thing we have to fear is fear itself nameless, unreasoning, unjustified terror which paralyzes needed efforts to convert retreat to advances. In every dark hour of our national life a leadership of frankness and vigor has met with that understanding and support of the people themselves which is essential to victory. I am convinced that you will again give that support to leadership in these critical days.
- 21) 1937 Cronin AJ: *The Citadel*. Boston: Little, Brown & Co, 1937. Example: https://www.antiqbook.com/search.php?action=search&author=CRONIN%20%20&title=The%20Citadel
- **22)** 1937 Farrow J: Damien the Leper. New York: Steel and Ward Inc., 1937. https://www.biblio.com/damien-the-leper-by-farrow-john/work/77302
- 23) 1939-10-19 Foster LR, Buchman S, Capra F: *Mr. Smith Goes to Washington*. Columbia Picture Corporation. https://www.dailyscript.com/scripts/MrSmithGoesToWashington.txt

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JEFFERSON

Just get up off the ground, that's all I ask. Get up there with that lady that is up on top of this Capitol dome--that lady that stands for liberty, take a look at this country through her eyes if you really want to see something and you won't just see scenery--you'll see the whole parade of what man's carved out for himself after centuries of fighting and fighting for something better than just jungle law, fighting he can stand on his own two feet-- free and decent, like he was created-- no matter what his race, color or creed. That's what you'll see. There's no place out there for graft or greed or lies or compromise with human liberties. And if that's what the grown-ups have done to this world that was given to them we'd better get those boy's camps started fast and see what the kids can do and it is not too late because this country is bigger than the Taylors, or you or me, or anything else. Great principles don't get lost once they come to light. They're right here. You just have to see them. ...

JEFFERSON (with effort)

I guess this is just another lost cause, Mr. Paine. All you people don't know about lost causes. Mr. Paine does. He said once they were the only causes worth fighting for, and he fought for them once, for the only reason that any man ever fights for them. Because of just one plain, simple rule, "Love thy neighbor," and in this world today, full of hatred, a man who knows that one rule has a great trust. You knew that rule, Mr. Paine, and I loved you for it, just as my father did. And you know that you fight for the lost causes harder than for any others. Yes, you'd even die for them, like a man we both know, Mr. Paine. You think I'm licked. You all think I'm licked. Well, I'm not licked and I'm going to stay right here and fight for this lost cause even if this room gets filled with lies like these, and the Taylors and all their armies come marching into this place. Somebody'll listen to me--some-- ...

- **24)** 1940 DeAngelis CD (Former Editor-in-Chief, *Journal of the American Medical Association*): Biography. Changing the face of Medicine. https://cfmedicine.nlm.nih.gov/physicians/biography 77.html
- **25**) 1942 Cronin AJ: *The Keys of the Kingdom*. Pub: Alfred Scherz Berne, 1942. https://www.abebooks.com/servlet/SearchResults?an=cronin&cm_sp=sort_-SRP--Results&fe=on&sortby=1&tn=keys%20kingdom
- **26**) 1944-06-25 Army Service Forces, Office of the Chief, Chemical Warfare Service, Gravelly Point, Washington, 25, D.C.

SPECIAL ORDERS)		25 June 1944
)	
No. 152)	

1. The Chief of Chemical Warfare Service commends the officers and enlisted men who voluntarily submitted to tests conducted by the Medical Division. These men participated beyond the call of duty by subjecting themselves to pain, discomfort, and possible permanent injury for the advancement of research in protection for our armed forces. Those named below knowingly submitted to exposure to chemical agents for some period during the months designated:

Page 534 of 1266

September and October, 1943

PVT. EARL L. ALEXANDER, JR, 35704460 PVT. EDWARD A. ALTMAN, 33783419 PVT. CHARLES H. ANDRUS, JR, 1919066...

PVT. CHARLES H. ANDRUS, JR, 1919066 was the father of Charles H. Andrus, III, M.D., F.A.C.S. Obituary of Charles Hiram Andrus, Jr., April 30, 1921 – December 21, 2013 https://www.legacy.com/us/obituaries/sfgate/name/charles-andrus-obituary?id=17958880

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ARMY SERVICE FORCES
                                                   OFFICE OF THE CHIEF, CHEMICAL WARFARE SERVICE Gravelly Point, Washington 25, D. C.
SPECIAL ORDERS '
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designated:
                                            September and October, 19h

PVT. EARL L. ALEXANDER, JR, 3570hh60

PVT. EDWARD A. ALTMAN, 33783h19

PVT. CHARLES H. ANDRUS, JR, 19190666

PVT. WENDELL M. BAKER, 39915577

PVT. JOHN J. BEREELLINI, 13128126

PVT. BILLY B. BIGGS, 1531311

PVT. EDWARD W. BOROWSKY, 13127887

FVT. GEORGE L. BROWNELL, 121701h1

PVT. WALTER E. BUTINSKY, 1317h719

PVT. CANON CHAM, h136627

PVT. GANON GHAM, h136627

PVT. FRANK B. CAVANAGH, 11091921

PVT. WILLIAM A. CHUPKA, 13127969

PVT. WILLIAM A. CHUPKA, 13127969

PVT. WILLIAM J. CLARK, 12153623

PVT. WILLIAM J. CLARK, 12253623

PVT. THOMAS A. CUSANO, 33782765

PVT. THOMAS A. CUSANO, 33782765

PVT. THOMAS A. CUSANO, 33782765

PVT. THOMAS N. DIGLETANO, 3685621

PVT. PAUL G. DODD, 357561h6

PVT. JAMES C. DOTHEY, h115h717

PVT. FRANCIS S. EURNSHEW, JR, 35756216

PVT. WILLIAM M. EPES, 12126987

PVT. WILLIAM M. EPES, 12126987

PVT. WILLIAM M. EPES, 12126987

PVT. VILLIAM M. EPES, 12126987

PVT. VILLIAM M. EPES, 12126987

PVT. VILPED F. FELGENDREGER, 33782398

PVT. TERRALL C. FR.NKS, 14154718
                                                                                       September and October, 1943
OCCUS 4500-189
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From 2015-06-22 Dickerson C: Secret World War II Chemical Experiments Tested Troops By Race. (World War II Secret Mustard Gas Testing) NPR s|t|l|p|r June 22, 2015. https://www.npr.org/2015/06/22/415194765/u-s-troops-tested-by-race-in-secret-world-war-ii-chemical-experiments The original document above was the first page of a thirty-one page document that can be accessed by the hyperlink in the NPR document: Attached was a long list of names.

- 27) 1944-10-25 Tillman B: The Gambier Bay's Final Hours. U.S. Naval Institute: Naval History Magazine 2019 Oct 33(5). https://www.usni.org/magazines/naval-history-magazine/2019/october/gambier-bays-final-hours
- **28)** 1946 Orwell G: *Animal Farm* New York: Harcourt, Brace and Company, 1946. https://www.worldcat.org/title/animal-farm/oclc/366597
- **29)** 1946-01-03 PL-79-293 authorizes the Department of Medicine and Surgery at the Veterans Administration. [2015-01-31We Served Too: VA history: VA's Department of Medicine and Surgery established. https://weservedtoo.wordpress.com/2015/01/31/va-history-vas-department-of-medicine-and-surgery-established/
- **30)** 1946-01-31 U.S. Department of Veterans Administration: Memorandum No. 2: Policy in Association of Veterans, Hospitals with Medical Schools. https://www.va.gov/oaa/Archive/PolicyMemo2.pdf
- **31)** 1948-12 Likert R: Public Opinion Polls. Why did they fail? A leading authority assays their weaknesses and suggests some tested new techniques that would improve their accuracy. Scientific American https://www.scientificamerican.com/article/public-opinion-polls/ (copy of article can be found in Scientific American.)

Dr. Likert developed his scale of attitudes to more simply define the general differences in attitudes of any given population using a scale that though arbitrary, had to show internal consistency. The scaling method demonstrated in the original paper a value in revealing general differences shown by different groups towards any subject with which they have dealings; thus revealing their tendencies only towards a particular response and not any specific measured result. Controversy surrounds the attempt to use statistical means to give more understanding to Likert scale data.

The controversy involves the use of parametric analysis for ordinal data. As described by Likert originally, the numerical scale that is used in association with the arbitrary numbers of his scale of attitudes allows for the scale to be internally consistent. The scale also should appear to be based on equal seeming differences so when applied to a random population the validity is not placed in question. It is because of this number scale that parametric data can easily be used and which then raises the concern if you should apply parametric analysis to a number set obtained through ordinal means.

Jamieson *et al.* (2004) reiterates that mean and mode should be used as a 'measure of central tendency' instead of mean and standard deviations as the later are inappropriate for ordinal data. There are non-parametric test that should be used simply because to use parametric analysis the data must be of interval or ratio level. Pell (2005) offers a different point that non-parametric analysis can be used given the 'assumptions are clearly stated and the data is of the appropriate size and shape.' He remarks that this analysis can provide useful insight but that caution should be exercised before arriving at statistical conclusions.

Although sound data cannot honestly be obtained from parametric analysis of ordinal data, it is agreed in the literature that meaningful results and trends can be obtained and that even a combination of the two means may be used to greater results. —Author unknown to Dr. Andrus-

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- 32) 1949 Orwell G: Nineteen Eighty-Four. London: Secker & Warburg, 1949. http://wordsmith.org/words/unperson.html
- **33)** 1951 Salinger JD: *The Catcher in the Rye.* Unknown date of a Study Guide by J.D. Salinger: The Catcher in the Rye Wisdom and Knowledge. https://www.shmoop.com/studyguides/literature/catcher-in-the-rye/quotes/wisdom-and-knowledge

Holden Caulfield: "You ought to go to a boy's school sometime. Try it sometime," I said. "It's full of phonies, and all you do is study so that you can learn enough to be smart to be able to buy a goddam Cadillac some day, and you have to keep making believe you give a damn if the football team loses, and all you do is talk about girls and liquor and sex all day, and everybody sticks together in these dirty little goddam cliques."

- **34)** 1953-1970 GE College Bowl. (TV 1958-1970). http://www.collegebowl.com/gecollegebowlresultrptdlg.asp
- 35) 1954 Huff D: How to Lie with statistics. https://online225.psych.wisc.edu/wp- content/uploads/225-Master/225-UnitPages/Unit-07/Huff StatisticsBook 1954.pdf
- 36) 1954 College of Physicians of Philadelphia: The History of Vaccines: Soviet trials of the Sabin's vaccine https://www.historyofvaccines.org/timeline#EVT 100330 and passive immunization https://www.historyofvaccines.org/content/articles/passive-immunization
- 37) 1955 Kennedy JF: *Profiles in Courage*. Chapter Six: "I looked down into my open grave..." Edmund G. Ross. New York: Harper & Brothers, 1955. Pages 126 - 151 https://archive.org/stream/in.ernet.dli.2015.460987/2015.460987.Profiles-In djvu.txt

...Those Kansas newspaper and political leaders who had bitterly denounced him in earlier years praised Ross for his stand against legislative mob rule: "By the firmness and courage of Senator Ross," it said, "the country was saved from calamity greater than war, while it consigned him to a political martyrdom, the most cruel in our history... Ross was the victim of a wild flame of intolerance which swept everything before it. He did his duty knowing that it meant his political death...It was a brave thing for Ross to do, but Ross did it. He acted for his conscience and with a lofty patriotism, regardless of what he knew must be the ruinous consequences to himself. He acted right."

- 38) 1956 Dooley TA: Deliver Us from Evil. New York: Farrar Straus Cudahy, 1956. Fischer JT: Dr. America – The Lives of Thomas A. Dooley, 1927 – 1961. https://archive.nytimes.com/www.nytimes.com/books/first/f/fisher-america.html
- **39)** 1956-05 Knowles J: A Separate Peace. First published in Cosmopolitan in May 1956... https://en.wikipedia.org/wiki/A Separate Peace
- 40) 1958 Chartered by Congress in 1958: Congressional Medal of Honor Society: Honor the sacrifice; inspire the future https://www.cmohs.org/news-events/commemoration/august-14- 1958-the-congressional-medal-of-honor-society-begins/

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- Gallantry in action. Intrepidity. Above and beyond call of duty. Risk of life. Selflessness. Exemplary action. Unwavering devotion. Conspicuous gallantry. Extraordinary heroism. The words enshrined with the Medal of Honor citations capture the best of what it means to be human.
- **41)** 1958-09-20 Peirce ER, Melville FS, Downie AW, Duckworth MJ: Antivaccinial gamma-globulin in smallpox prophylaxis. The Lancet 1958 September 20: 272 (7047); 635-638. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(58)90351-9/fulltext; https://www.sciencedirect.com/sdfe/pdf/download/eid/1-s2.0-S0140673658903519/first-page-pdf
- **42)** 1959 Haas D, Pellicer JL (illustrator): *Men of Science*, A Badger Book. (Racine, Wisconsin: Whitman Publishing Company, 1959) 9-17, 73-79. https://www.amazon.com/Badger-Book-Men-Science/dp/B000GBQ9ZI
- **43)** 1959-01 Gordon VH: The use of gamma globulin In Infectious Disease. J Ark Med Soc 1959 Jan; 55(8): 299-303. https://journals.sagepub.com/doi/pdf/10.1177/216507995900700407
- **44)** 1959-07-11 Semple AB, Parry WH, Hobday TL: Antivaccinial gamma-globulin; a further report on smallpox prophylaxis. Lancet 1959 Jul 11; 2(7089): 34. https://pubmed.ncbi.nlm.nih.gov/13673585/
- **45)** 1959-10 Fellows EW: 'PROPAGANDA:' HISTORY OF A WORD. American Speech 1959 Oct; 34 (3): 182 189. https://www.jstor.org/stable/454039
- **46)** 1960 Magnuson PB: *Ring the Night Bell—an American surgeon's story*, Chapters 18-19. Boston: Little, Brown and Company, 1960. Pages 276-305. https://www.amazon.com/Ring-Night-Bell-Autobiography-Surgeon/dp/B002ZTENN4
- **47)** 1960 University of Cincinnati: Sabin Sunday, 1960. https://magazine.uc.edu/issues/0408/on_campus.html
- **48)** 1961 Kempe CH, Bowles C, Meiklejohn G, Berge TO, St. Vincent L, Sundara Babu BV, Govindarajan S, Ratnakannan NR, Downie AW, Murthy VR: The use of vaccinia hyperimmune gamma-globulin in the prophylaxis of smallpox. Bull. Wld Hlth Org. 1961; 25: 41-48 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2555541/pdf/bullwho00317-0052.pdf

This paper records an attempt to assess the prophylactic value of immune gamma-globulin, prepared from the serum of recently vaccinated adults, in the protection of close contacts of smallpox in Madras. The results serve to confirm findings of a previous study made in Madas in 1953, and show that the incidence of smallpox in close contacts given immune gamma-globulin prophylactically was about a quarter of that in the control contacts who received no such passive immunization—a statistically significant difference. Because of the limited supply of immiune gamma-globulin, is likely that its prophylactic use will be restricted to those especially at risk, for example, close unvaccinated family contacts, newborn infants and pregnant women.

- 49) 1961-01-20 Kennedy JF: Inaugural Address. https://www.youtube.com/watch?v=PEC1C4p0k3E
- **50)** 1962 Boucher A, Tehan J: Prince of Democracy: James Cardinal Gibbons. Garden City New York: Hanover, 1962. https://www.biblio.com/book/prince-democracy-james-cardinalgibbons-boucher/d/1399934855
- 51) 1962-01-01 Marennikova SS: The use of hyperimmune antivaccinia gamma-globulin for the prevention and treatment of smallpox. Bull. Wld Hlth Org. 1962; 27: 325-330. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2555760/pdf/bullwho00308-0017.pdf/?tool=EBI
- 52) 1962-04-28 Hobday TL, Lpool MB: Antivaccinial gamma-globulin in the control of smallpox. The Lancet April 28, 1962; 279 (7235): 907-908. https://pubmed.ncbi.nlm.nih.gov/13907883/

It therefore seems that antivaccinial gamma-globulin can be an effective agent in the prevention of smallpox where contacts are detected too late for vaccination to afford protection; it can never supplant vaccination, but is complementary and may succeed where vaccination must

53) 1963-06-10 Kennedy JF: Commencement Address at American University. https://www.jfklibrary.org/archives/other-resources/john-f-kennedy-speeches/americanuniversity-19630610

> So, let us not be blind to our differences--but let us also direct attention to our common interests and to the means by which those differences can be resolved. And if we cannot end now our differences, at least we can help make the world safe for diversity. For, in the final analysis, our most basic common link is that we all inhabit this small planet. We all breathe the same air. We all cherish our children's future. And we are all mortal.

- 54) 1964-01 Kempe CH: The use of vaccinia hyperimmune gamma-globulin in the prophylaxis of smallpox. World Health Organization, Expert Committee on Smallpox, Geneva, 14-20 January 1964. https://apps.who.int/iris/bitstream/handle/10665/67693/Smallpox WP 4.pdf?sequence=1
- 55) 1964 Title VI, Civil Rights Act of 1964 application in the exclusive administration of experimental monoclonal antibodies against COVID-19 preferetially to President Trump, HUD Secretary Carson, former Governor Christie, and former New York mayor Rudolph Giuliani in deference to the USA populous. https://www.dol.gov/agencies/oasam/regulatory/statutes/title-vi-civil-rights-act-of-1964
- 56) 1967-08 Andrus CH entered Saint Ignatius College Prep. AMDG: What does A.M.D.G. mean? https://www.siprep.org/about-us/ou-missions/amdg

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- 57) 1967 Director Jack Webb: Dragnet: Juvenile D-32 -- Child bitted by an unknown dog and a race for time regarding need for Rabies anti-venom. Dragnet 1967, Season 3, Episode 24 https://www.youtube.com/watch?v=4nOyaWaNBUQ
- 58) 1968 Faherty, WB, S.J.: Better the Dream—Saint Louis University & Community, 1818-1968. St. Louis University MCMLXVII, A Sesquicentennial Edition. https://www.abebooks.com/servlet/BookDetailsPL?bi=1401355432&cm_mmc=ggl--COM Shopp Rare- -product id=bi%3A%201401355432- keyword=&gclid=EAIaIQobChMImsnAl9av9AIV18mUCR3HPwKHEAOYASABEgJovfD
- **59)** 1969 Kübler-Ross E: On Death and Dying. New York: MacMillian Publishing Co., 1969 https://www.goodreads.com/book/show/781844.On Death and Dying
- 60) 1969-04: Tierney TM, Director, Bureau of Health Insurance. Bureau of Health Insurance Intermediary Letter No. 372 can be found on pages 1870 – 1877 of Irregularities in the Salt Lake City, Utah, Veterans' Hospital and Other Stations, Committee on Veterans Affairs, U.S. House of Representatives: Irregularities in the Salt Lake City, Utah, Veterans' Hospital and Other Stations. U.S. House of Representatives Committee on Veterans Affairs, 91st Congress, 1st Session, House Committee print no. 167, part I, December 19, 1969: 1 – 2247. https://books.google.com/books?id=ZEAWAAAAIAAJ&pg=PA1685&lpg=PA1685&dq=irr egularities+in+the+Salt+Lake+City,+Utah,+veterans%27+hospital+and+other+stations,+Sep tember+21,+1970&source=bl&ots=Rq38I 0fbD&sig=ACfU3U0Xt7RDQUZPuyLD6awYLd -RXu4NA&hl=en&sa=X&ved=2ahUKEwjL8vsqr0AhWil2oFHZfTBxsO6AF6BAgNEAM#v=onepage&q=irregularitie

%20in%20the%20Salt%20Lake%20Citv%2C%20Utah%2C%20veterans'%20hospital%20an d%20other%20stations%2C%20September%2021%2C%201970&f=false

BUREAU OF HEALTH INSURANCE INTERMEDIARY LETTER NO. 372

Subject: Part B payments for services of supervising physicians in a teaching setting.

From questions which have been raised and from our onsite reviews, there appears to be a serious need to obtain a better and more uniform understanding among carriers, providers, and physicians of the conditions under which payment may be made under Part B for services rendered to patients by supervising physicians in the teaching setting and the method for determining the reasonable charge which may be recognized for such services. The enclosed guidelines are intended to clarify and supplement the criteria that govern reimbursement in this area as reflected in §§ 6102.7, 6335, and 6720 ff. of the Part B Intermediary Manual.

⁻⁻ May 30, 2022 -----This is a COVID-19 Timeline Bibliography for Educational Purposes <u>ONLY</u> in the presentation of this information before the people of the United States of America (U.S.A.) the World and proof-first the Parist of States. of America (U.S.A.), the World, and specifically the President of the U.S.A. without any compensation to the author. All submissions including this timeline bibliography can be obtained under the Freedom of Information Act (FOIA) by formally requesting a copy of NIAID Case #12276 from the FIOA Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

1979

Carriers are urged to review their present reimbursement practices in light of these guidelines and to take appropriate action as soon as possible to bring practices into conformity with the guidelines. The Part B Informediany Manual will be revised to incorporate these clarifications and additions.

THOMAS M. TIERNBY,
Director, Bureau of Health Insurance.

PART B PAYMENTS FOR SERVICES OF SUPERVISING PHYSICIANS IN A TEACHING SETTING

A. Conditions which must be met for a leaching physician to be eligible for Part B reimburses ent as an attending physician. The eligible for Part B reimburses ent as an attending physician.

The physician is must be the patient's "attending physician." This means he must, as demonstrated by performance of the activities isted below, render sufficient personal and identifiable metital services to the Medicare beneficiary to exercise full, personal control over the management of the portion of the case for which a charge can be recognized to the personal shift better must be of the same character, in terms of the responsibility patient must be of the same character, in terms of the responsibility patient must be of the same character, in terms of the responsibility physician." For an entire period of hospital care, the feating physician must as a minimum:

(a) review the patient's history, the record of examinations and tests in the institution, and make frequent reviews of the patient's progress; and

(b) personally examine the patient; and
(c) confirm or review the diagnosis and determine the course of treatment to be followed; and

(c) citier perform the physicians' services required by the patient or supervise the treatment so as to assure that appropriate services are provided by interns, residents, or others and that excites are provided by interns, residents, or others and that excites are provided by interns, residents, or others and that of the physician is a nonteaching setting when a major surgical procedure or a complex or dangerous medical procedure is performed; for the physician to be an "attending physician is performed; for the physician to be an "attending physician and be presentally responsible for the continuity of the patient's care, alternst throughout the period of hospitalization.

(f) be recognized by the patient as his personal physician and be personally responsible for the continuity of the patient's care, alternst throughout the period of hospitalization.

7) The term "nhysiciam" does not include any resident or inters of the hospital regardless of any other title by which he is designated or his position on the needest staff. For example, a separate physiciam would staff the consuler of the physiciam would still be considered a resident since the senior year of the resident is essential to completion of the program.

1974

4. The services of a teaching physician while visiting patients during grand rounds is basically teaching and does not contribute to an "attending" relationship with any of the patients visit of the patients of the patient of patients of the patient of patients carefully the house staff. It is only through his direct personal involvement with a patient data of large may be resognized under Part B. Such an involvement would necessarily include personal examination of the patient as well as direction of and responsibility for the treatment provided.

involvement would necessarily include personal examination of the patient as well as direction of and responsibility for the treatment provided.

B. Determining the amount payable under part B

1. The amount paid for direct medical services rendered by the teaching physician should be related to only that discrete portion of the patient's care for which the physician exercised the pertinent responsibilities of an attending physician outlined in A.I. For example, if the patient's care for which the physician carcissed the pertinent responsibilities of an attending physician outlined in A.I. For example, if the patient's personal physician for the physician becomes the attending physician only with respect to the impatient care, the lesser extent of the teaching physician's service should be taken into account in recognizing a charge; otherwise the out-of-bospital service would be billed for and paid twice. Similarly, if surgery was performed and the teaching physician rendered identifiable personal service to the patient in the operating room, it is necessary to determine whether that physician performed services more nearly analogous to a consultant, an assistant at surgery (see first "Example" in part A), or as the "attending" surgeon in order to identify the appropriate reasonable charge. If the physician acted as the attending surgeon but did not render the pre- or post-surgient services generally performed by a private surgeon to a private patient, the difference in service should be reflected in the amount of reimbursement.

2. The following conditions should be taken into account in determining the "euclorismy" charges of teaching physicians for services which they oracide as attending physicians to Medicare beneficaries.

(a) If the teaching setting (i.e., more than half of the time spent in the practice of medicaries as patients before they were hospitalized or who were referred to him by physicians responsible for their care outside the hospital setting (iffer from those in the outside the hospital set

Example.—A supervising physician carried out all of the activities listed above for a surgical patient but (e). He was not present in the OR when the major surgery was performed because supervision of proceedings of the proceeding the operation was not required. All physicians resident performing the operation was not required. All physicians criterion (e) was not not. Therefore, the surgical proceedings because criterion (e) was not not. Therefore, the surgical proceedings physician for the period of brospital care although he might meet the criteria listed in A.2. below and be held as the attending physician for sortion of the care provided.

Even if the supervising physician chose to be present in the OR, payment could not be made to him for the surgical procedure since his presence was not medically necessary and he could not, therefore, function as the attending physician in connection with the surgery However, if he was scrubbed and acted as an assistant, payment could be made to him as a surgical assistant if such an assistant, as needed and another resident or physician did not fill the role (see ifem A.2. below).

and another restricts or physician was present a surgery, and the surgery below).

If the supervising physician was present at surgery, and the surgery was performed by a resident acting under his close supervision and instruction, he would not be the attending surgeon unless it were customary in the community for such services to be performed in a similar fashion to private patients who pay for services rendered by available abusician.

customary in the community for such services to be performed in a similar fashion to private patients who pay for services rendered by a private physician.

Example—Agroup of physicians share the teaching and supervision of the house staff on a rotating basis. Each physician sees patients every third day as he makes rounds. No physician can be held to be one of these patients attending physician for any portion of the hospital care although consultations and other services they personally perform for the patient might be covered.

2. A teaching physician may be held to be the attending physician for a portion of a patient's hospital stay: if the portion is a distinct segment of the patient's course of treatment (e.g., the pro-perative or poet-operative period) and of sufficient duration to impose on the physician a substantial responsibility for the continuity of the patient's care; if the physician, as a minimum, performs all of the activities described above with respect to that portion of the stay and if the physician is recognized as the patient's physician is not format to be the stay. If a teaching physician is not format to be the same of the stay, it is teaching to a patient's stay, he may not be reimbursed for any so a portion of the patient for my so to portion of the stay in the patient.

Example—A physician carried out all of the activities listed above for a surgical patient mild midway in the post-operative period, when the physician's teaching from of duty ended. Since he was not responsible for the continuing care of the patient throughout the post-operative period, when the physician for that period.

Example—A propried for a full sended. Since he was not responsible for the continuing care of the patient throughout the post-operative period, when the physician for that period.

period.

3. Performance of the activities referred to above must be demonstrated, in part, by notes and orders in the patient's records that are either written by or countersigned by the supervising physician.

1875

1875

Example.—A hospital with an approved teaching program receives payment for physicians' services rendered to 80 percent of its non-Medicare patients. Fifty percent are paid for by public assistance as the services are paid for by public assistance as the services are paid for by public assistance as the service and the area of the services are paid for by public assistance as the service and the area of the service and the service and the service and the service and the service as the service which the service should serve as the basis for determining the teaching physicians' customary charges for Medicare.

(c) Where neither the physician nor the provider has established charges for helpsysician's services which are in effect for non-Medicare patients, the carrier and intermediary must make the necessary charge and cost determination based on that portion of the physician's compensation which is for services to patients, determined pursuant to the regulations proverning rembursement for the services of provider-lased physicians remove the services of provider-lased physicians.

3. Where teaching physicians of a hospital, billing through a hospital or other organization, adopt a uniform schedule of clarges for the purpose of billing under Part B for the services they provide as attending physicians in the teaching setting, carrier acceptance of the schedule for reimbursement purposes should be lassed on a finding that the schedule does not exceed the average of reasonable charges which would be determined if each physician were individually reimbursed his reasonable charge for the services involved.

4. In determining the number of visits which may be considered reasonable, e.g., in a course of freatment for which a global fee is not ordinarily charged, the total number of visits which and the caching purposes. Similarly, total reasonable charges for a course of treatment in the teaching setting should be compared with and

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

mining whether the compensation level is reasonable for the supervisory and teaching services alone and insufficient to cover patient careservices as well. The carrier and intermediary should make this fluding jointly.

Example.—An employment agreement between a physician and the hospital states that he will be paid \$50,000 a year for administration, supervision and teaching. However, he spends one-half of his time in providing patient care. The carrier and intermediary determined that if his compensation were allocated solely to the time the physician spent in the performance of his hospital duties, it would yield an hourly rate of compensation what double the rate paid for similar work elsewhere in the area. Therefore, the carrier and intermediary concluded that only a portion of the compensation was for hospital activities and reimbursable under Part A. Since charges were not customarily billed for the medical services the physician provide, the remainder would serve as a basis for computing the physician provide, the remainder would serve as a basis for computing the physician's reasonable charges for patient care in accordance with B.3.b. above.

Carrier responsibilities for claims review and verification

Carrier responsibilities for claims review and verification

Carrier responsibilities for claims review and verification

1. The carrier is responsible for assuring that the bills being submitted were prepared with an understanding of the conditions governing payment for physicians' services in the teaching setting.

To help carry out this responsibility, carriers will not pay bills (SSA-1490 or SSA-1561) for services rendered in the teaching setting in any month after May 1969, unless:

(a) the clief of the department or service involved certifies on a form furnished by the carrier that each of the billed services for that month meets the pertinent requirements of A.1.; or

(b) the bill has been signed by the attending physician and he understands that he is certifying that he met the requirements for those services for which the claim is made.

2. The provision of personal and identifiable services must be substantiated by appropriate and adequate recordings entered personally by the physician in the hospital or, in the case of outpatient services, outpatient clinic chart. The carrier is expected as part of its responsibilities to make appropriate checks of patient records, examining admission, progress, and discharge notes to verify that services for which charges are billed met the appropriate steps should be taken to adjust the reinbursement.

3. Bills must indicate when services are furnished in the teaching the services in the teaching of the work of the new content and and the properties and the teaching of the work of the new content and and the properties and attention to the teaching of the work of the new content and and the properties are desirable in the teaching the services in the teaching of the work of the new content and and the properties are desirable to the teaching at the properties and attention and the properties of the new content and the properties and attention to the properties and attention to the properties and the properties are desirable and the teaching at the properties and attention to the properties and attention to the properties and

not meet the criteria, appropriate steps snound be made no adjust the reinhursement.

3. Bills must indicate when services are furnished in the teaching setting, the name of the provider and attending physician involved, and the extent of the services provided as an attending physician. The services must be defined and quantified to avoid errors in applying the reasonable charge limitation—e.g., to avoid applying the reasonable charge for a global service where only the surgical procedure or another component service was provided as an attending physician.

4. The carrier will need to carry out the steps necessary to assure itself that have shedule of charges proposed for the teaching setting is actually applied and collected.

D. Who may bill

D. Who may bill

Where the supervising physician is a member of a group which provides teaching services in a hospital, the Part B payment for services rendered as aftending physicians by the group may be billed for:

1. by the physician or a corporation, partnership, or other organization of physicians (including an association of teaching physicians organized for the purpose of billing for and distributing insurance monies and other payments received for professional services to patients) on form 1490;

2. by the hospital on form 1554 provided that the carrier has determined that the certification described in C.1.a. has been executed and compiled with; and

3. if the services are performed by a physician who is a faculty member of a medical, osteopathic, or dental school, by the school on form 1490.

1490.

The individual physician's authorization is required to be on file in writing with the hospital or other organization to permit any of the above organizations to bill on his behalf. The organization must furnish to the Part B carrier the names of the physicians who have authorized the organization to bill on their behalf, and must agree to keep the carrier informed on a current basis of changes in membership in the group.

FEBRUARY 11, 1970

Washington, D.C., January 28, 1970.

WASHINGTON, D.C., January 28, 1970.
To: Director, Investigation and Security Service.
From: K. F. Everett, Special Investigator.
Subject: Alleged Irregularities in Payroll Practices at VAII, Nashville, Tenuessee.
Period of Investigation: December 4, 1969 to December 16, 1969 and January 5, 1970 to January 9, 1970.

I. Authority

Investigation was authorized by the Deputy Administrator on November 28, 1969.

II. Matter investigated

II. Matter investigated

 During a visit of an Internal Audit Service team at VAII, Nashville on another matter, information was developed that Radiology Service was establishing and maintaining Time and Attendance records for Residents and student Technicians who are not working for VA and that this appeared to be done for the purpose of generating funds for these persons or the Medical Center at the expense of appropriated funds.

printed funds.

2. Bobby Moore, Management Specialist, Internal Audit Service, assisted in the investigation.

III. Narvative summary

 Hospital records show that on July 30, 1969, a contract was entered into between the Nashville VAII and the Vanderbilt University to furnish five full-time Physicians from the Vanderbilt Department of Radiology to furnish radiology services to the VAII through June 20, 1970 at a cost of \$117,300.00 per annum. The contract stipulates

61) 1969-09-03 Comptroller General of the United States: Report to the Committee on Finance United States Senate—Medicare payments for services of supervisory and teaching physicians at Cook County Hospital, Chicago, Illinois B-164031(4). National Library of Medicine, Bethesda 14, MD. W 275 AI3 U5m 1969

https://books.google.com/books?id=TVAsAAAAIAAJ&pg=PP5&lpg=PP5&dq=Medicare+P ayments+for+Services+of+Supervisory+and+Teaching+Physicians+at+cook+county+hospita 1,+chicago,+illinois+b-

164031(4)&source=bl&ots=sSRW70DaNv&sig=ACfU3U3Drb4swZ19p-w3yqjYXpFinegmA&hl=en&sa=X&ved=2ahUKEwjS5rOp86r0AhUDZc0KHZtaBDMO6AF6BAgEE AM#v=onepage&q=Medicare%20Payments%20for%20Services%20of%20Supervisory%20 and%20Teaching%20Physicians%20at%20cook%20county%20hospital%2C%20chicago%2 C%20illinois%20b-164031(4)&f=false

Includes:

Response of Robert Freeark, M.D., Director, Associated Physicians of Cook County Hospital in a letter of July 3, 1969 to Mr. David Hanna, US GAO, pages 89-91 and Thomas Tierney, Director, Bureau of Health Insurance: Bureau of Health Insurance, Intermediary Letter No. 372.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

APPENDIX V Page 1

COOK COUNTY HOSPITAL

MLLIAM H. HARVEY, COMMISSIONER

1825 WEST HARRISON STREET CHICAGO, ILLINOIS 60612 PHONE: AREA CODE 312 - 633-6000 ROBERT J. FREEARK. M.D. FRED A. HERTWIG

July 3, 1969

Mr. David Hanna United States General Accounting Office 610 South Canal Street Chicago, Illinois

Dear Mr. Hanna:

This will acknowledge my recent meeting with you and the opportunity it provided to review the rough draft of a proposed report by the General Accounting Offices. Other than the minor corrections which you have agreed to make, I would also ask that you make two major additions.

One of the issues which the study raises is the extent to One of the issues which the study raises is the extent to which attending physicians are providing supervision and direction to internes and residents. While I would agree that in many instances this supervision and direction is poorly documented in the medical record, this does not mean that it was not given. In many private hospitals, the only notation in a hospital chart to indicate that a physician visited a patient or performed a procedure, is that which appears in the nurses notes. We simply do not have enough nurses to provide this documentation and it is not realistic to expect this to be done by the physician is not realistic to expect this to be done by the physicians. I believe the vast majority of "undocumented services" were so categorized because neither a doctor's or a nurse's note records a visit.

I believe Recommendations #31 and #36 of the report of the Joint Commission on Accreditation of Hospitals (February 1968) should be included in your report. These statements and the fact that our interneship and residency training programs are fully approved by the Council on Medical Education of the American Medical Association, is ample evidence that attending physicians are providing supervision and direction to our house staff. There is no doubt in my mind that patient care in a "Teaching Hospital" (one that conducts approved residency and interne training programs) is under greater scrutiny and better supervised than in hospitals without these programs.

----- May 30, 2022 -----

APPENDIX V Page 2

Mr. David Hanna

2.

July 3, 1969

These statements by the Joint Commission are pertinent to a thorough understanding of conditions at the hospital. In part, they constitute an explanation of why documentation of services rendered is so difficult.

why documentation of services rendered is so difficult.

My second request would be to ask that you include in your report my opinion as to the basis for compensation for salaried physicians at Cook County Hospital. This is in part a matter of semantics and has led to considerable misunderstanding. The concept that salaried physicians are not paid for patient care, but for their administrative and supervisory duties is predicated on the fact that over 50 percent of our salaried staff carry an extraordinary administrative and educational work load. An estimated 50-70% of these salaried physicians are expected to supervise a large number of medical and non-medical personnel in activities not directly related to the care of the individual patient. (e.g., there are only two salaried positions for general surgery. These two men are administratively responsible for the assignment and education of 72 attending physicians, 62 general surgical residents, and an average of 30 internes and 42 medical students. This personnel changes regularly on the five general surgical wards that have a total bed capacity of over 300 patients. In addition, one of the two full time surgeons is also the Director of the Blood onk, which has 23 technical persons in its employ.)

Bank, which has 23 technical persons in its employ.)

Furthermore, at the present time, the salary paid to over 60 percent of our full time staff represents only a portion (estimate 60%-70%) of their total professional income. In addition, this salary is approximately two-thirds that paid to physicians in comparable positions in hospitals in this geographic area. Based on the extraordinary administrative and formal educational responsibilities and the concept of a partial salary for a portion of their time, I am of the opinion that when

> APPENDIX V Page 3

Mr. David Hanna

3. July 3, 1969

the majority of our salaried physicians go to the individual patient's bedside or to the operating room, they are providing professional services for which they are not compensated by the salary they receive from Cook County Hospital. This is consistent with the Civil Service rating which they hold as attending physicians, caring for patients without compensation.

I hope that you will see that this information is included in your report and I wish to thank you for the considerate manner in which you have carried out your activities.

Robert Dwallew

RJF/ubd

----- May 30, 2022 -----

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- **62)** 1970 Anderson SG, Skegg J: The international standard for anti-smallpox serum. Bull. Wld Hlth Org 1970; 42: 515-523. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427467/pdf/bullwho00215-0018.pdf
- 63) 1970-02-11 Comptroller General of the United States: Regarding the GAO report of alleged overpayment to The Associated Physicians of the Cook County Hospital, B-164031(4) https://www.gao.gov/assets/b-164031%284%29-089860.pdf
- 64) 1973-04-28 U.S. Department of Health, Education, and Welfare, Public Health Service: FINAL REPORT of the Tuskegee Syphilis Study Ad Hoc Advisory Panel. https://biotech.law.lsu.edu/cphl/history/reports/tuskegee/complete%20report.pdf
- 65) 1974-06-15 Bernstein C, Woodward b: *All the President's Men.* New York: Simon & Schuster, 1974. https://en.wikipedia.org/wiki/All the President%27s Men
- **66)** 1977 Dallin A: Communism. The World Book Encyclopedia, Ci-Cz, Volume 4, Field Enterprises Educational Corporation, Chicago, 1977. P 724b-727.

Why Communism? The spread of Communism is usually thought of in terms of force and revolution. However, millions of persons have freely chosen to become Communists or to vote for them.

Communism has different appeals for different individuals and groups. Its main attraction for some is its claim to provide simple answers and solutions in difficult situations. Some persons join the party to avoid being outsiders, and to feel they are part of a meaningful group. Others join to ride the "wave of the future." They believe that Communist victory is inevitable.

The appeals of Communism seem to be strongest in countries where some of the following conditions exist. (1) There are huge differences in income and social position between the poor and rich, and the poor feel these differences. (2) Communism is the only effective movement fighting for change, reform, or revolution. (3) The existing government does not command the strong loyalty of the people, and its institutions do not stand up well under stress. (4) Many persons feel deprived and discriminated against socially and economically, and as national or racial groups. (5) Communists are not looked on as criminals or lunatics, but as one of several accepted types of revolutionaries.

- 67) 1978 Brandt AM: Racism and Research: The case of the Tuskegee syphilis study. The Hastings Center Report 1978; 8(6): 21-29. https://dash.harvard.edu/bitstream/handle/1/3372911/Brandt_Racism.pdf?sequence=1&isAllowed=y
- **68)** 1979-04-01 FEMA founded. https://www.fema.gov/
- **69)** 1979-04-18 Office of the Secretary, The National Commission for the Protection of Human Subjects of Research. The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html

- **70)** 1980 38 U.S.C. § 5705: Protection of Morbidity and Mortality conferences from legal discovery. https://www.law.cornell.edu/uscode/text/38/5705
- 71) 1981-04 Busuttil RW, Davidson RK, Fine J, Tompkins RK: Effect of prophylactic antibiotics in acute nonperforated Appendicitis A prospective, randomized, double-blind clinical study. Ann Surg, Oct 1981; 194 (4): 502-509. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1345331/pdf/annsurg00212-0140.pdf

Table 9. Postoperative Infections

	Number	Per Cent
Group I (Placebo)	6/45	13.3
Group II (cefamandole preop)	1/46	2.2
Group III (cefamandole and carbenicillin preop)	0/45	0

This one study was extremely influential in the discontinuation of all placebo antibiotic studies. Subsequently all studies have been comparison studies between the new antibiotic with established antibiotics.

- **72)** 1986-06 Hyslop JW, Maull KI: Natural history of the retained surgical sponge. South Med J 1986 Jun; 75(6): 657-660. https://pubmed.ncbi.nlm.nih.gov/7089613/
- 73) 1982-06-24 U.S. Supreme Court: Nixon v. Fitzgerald, 457 U.S. 731 (1982), No. 79-1738, Argued November 30, 1981, Decided June 24, 1982. https://supreme.justia.com/cases/federal/us/457/731/
 - 2. Petitioner, as a former President of the United States, is entitled to absolute immunity from damages liability predicated on his official acts. Pp. 457 U. S. 744-758.
 - (a) Although there is no blanket recognition of absolute immunity for all federal executive officials from liability for civil damages resulting from constitutional violations, certain officials -- such as judges and prosecutors -- because of the special nature of their responsibilities, require absolute exemption from liability. *Cf. Butz v. Economou*, 438 U. S. 478. Determination of the immunity of particular officials is guided by the Constitution, federal statutes, history, and public policy. Pp. 457 U. S. 744-748.
 - (b) The President's absolute immunity is a functionally mandated incident of his unique office, rooted in the constitutional tradition of the separation of powers and supported by the Nation's history. Because of the singular importance of the President's duties, diversion of his energies by concern with private lawsuits would raise unique risks to the effective functioning of government. While the separation of powers doctrine does not bar every exercise of jurisdiction over the President, a court, before exercising jurisdiction, must balance the constitutional weight of the interest to be served against the dangers of intrusion on the authority and functions of the Executive Branch. The exercise of jurisdiction is not warranted in the case of merely private suits for damages based on a President's official acts. Pp. 457 U. S. 748-754.
 - (c) The President's absolute immunity extends to all acts within the "outer perimeter" of his duties of office. Pp. 457 U. S. 755-757.

(d) A rule of absolute immunity for the President does not leave the Nation without sufficient protection against his misconduct. There remains the constitutional remedy of impeachment, as well as the deterrent effects of constant scrutiny by the press and vigilant oversight by Congress. Other incentives to avoid misconduct may include a desire to

Page 457 U.S. 733

earn reelection, the need to maintain prestige as an element of Presidential influence, and a President's traditional concern for his historical stature. Pp. 457 U. S. 757-758.

74) 1983-05 Williams GR: Presidential Address: A history of appendicitis with anecdotes illustrating its importance. Ann Surg 1983 May; 197 (5): 495-506. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1353017/pdf/annsurg00135-0007a.pdf (This citation is listed regarding page 504 in which the "teaching at the bedside" is epitomized by Dr. William Halsted (father of American Surgery) and Dr. William Osler (father of American Internal Medicine) weighing in on the appendicitis of Dr. Harvey Cushing (father of American Neurosurgery):

On September 9, 1987, Dr. Harvey Cushing, then a resident in Surgery at The Johns Hopkins Hospital, operated on a patient with a ruptured appendix. The patient died ten days later of peritonitis. This experience must have increased his apprehension when, on Sunday, September 26, 1897, Cushing experienced abdominal pain and carefully recorded the development of his own episode of acute appendicitis (Fig. 14). At 9:00 am the following morning, he was seen in consultation by Drs. Halsted and Osler who did not advise operation. At 2:00 pm on the same day, he was taken to the operating room where Dr. Halstead removed his appendix. A somewhat complicated recovery followed (fig. 15).

- 75) 1985-11-28 Anderson RM, May RM: Vaccination and herd immunity to infectious diseases. Nature 1985; 318: 323-329. https://www.nature.com/articles/318323a0.pdf
- **76)** 1986-08 Condon RE: Type III Error. *Arch Surg.* 1986;121(8):877-878. doi:10.1001/archsurg.1986.01400080019002 https://jamanetwork.com/journals/jamasurgery/article-abstract/591890

Type I and type II errors are the two classic pitfalls in statistical analysis: finding a difference when there is none (type I) and failure to find a true difference (type II). There is, in addition, another important error that regularly appears in scientific journals. This error, the type III error,¹ occurs whenever the conclusions drawn are not supported by the data presented. In recent years, type III errors have been increasing in prevalence. Some illustrations drawn from recently published articles should serve to define my point. I have deliberately omitted citation of sources because my intent is to illustrate, not embarrass.

- 77) 1987 Cohen SN: Chapter 37: Immunization-Passive Immunization. *Basic & Clinical Immunology*, 6.th Edition. Stites DP, Stobo JD, Wells JV (eds), Norwalk, CT/Los Altos, CA: Appleton & Lange, 1987. Pages 669-673.
- **78)** 1987-11-12 Trump DJ with Tony Schwartz: *TRUMP The Art of the Deal*. New York: Random House, 1987. http://www.randomhousebooks.com/books/180675/

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Please note that the words "sorry" or "apologize" are not mentioned even once in this book.

- 79) 1990-04 Mullis KB: The unusual origin of the Polymerase Chain Reaction. A surprisingly simple method for making unlimited copies—during a moonlit drive through the mountains of California. https://cs.brown.edu/courses/csci1810/resources/pcr%20origin.pdf
- 80) 1992 Chard T: Review: Pregnancy tests: a review. Human reproduction 1992; 7 (5): 701-710. https://academic.oup.com/humrep/articleabstract/7/5/701/631514?redirectedFrom=fulltext
- **81)** 1993 U.S. Institute of Medicine: Veterans at Risk—The Health Effects of Mustard Gas and Lewisite. Institute of Medicine (US) Committee on the Survey of the Health Effects of Mustard Gas and Lewisite. Constance M Pechura and David P Rall., eds. (Washington, D.C.: National Academies Press, 1993). https://www.ncbi.nlm.nih.gov/books/NBK236070/ and https://www.nap.edu/catalog/2058/veterans-at-risk-the-health-effects-of-mustard-gas-and
- 82) 1993-05 Stark A: What's the matter with business ethics? Harvard Business Review, May-June1993. https://hbr.org/1993/05/whats-the-matter-with-business-ethics

And yet, I suspect that the field of business ethics is largely irrelevant for most managers. It's not that they are hostile to the idea of business ethics. Recent surveys suggest that over three-quarters of America's major corporations are actively trying to build ethics into their organizations. Managers would welcome concrete assistance with primarily two kinds of ethical challenges: first, identifying ethical courses of action in difficult gray-area situations (the kind that Harvard Business School Lecturer Joseph L. Badaracco, Jr. has described as "not issues of right versus wrong," but "conflicts of right versus right"); and, second, navigating those situations where the right course is clear, but real-world competitive and institutional pressures lead even well-intentioned managers astray.

Henning PJ: When money gets in the way of corporate ethics. The New York Times, DealBook/Business & Policy, April 17, 2017. https://www.nytimes.com/2017/04/17/business/dealbook/when-money-gets-in-the-way-ofcorporate-ethics.html

- 83) 1993-06-03 Dingell JD: Shattuck Lecture Misconduct in Medical Research. N Engl J Med 1993 June 3; 328(22): 1610 – 1615. https://www.nejm.org/doi/pdf/10.1056/NEJM199306033282207?articleTools=true
- 84) 1993-07 Allen JB: Possessed. https://archive.org/details/possessedtruesto00alle/page/n5/mode/2up
- 85) 1995 Casadevall A, Scharff MD: Return to the past: the case for antibody-based therapies in infectious disease. Clin Infect Dis 1995; 21(1): 150-161. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7197598/pdf/21-1-150.pdf
- 86) 1995 Mudd R: Last secrets of the Axis. https://www.youtube.com/watch?v=d5ARbOVpFqc ----- May 30, 2022 -----This is a COVID-19 Timeline Bibliography for Educational Purposes <u>ONLY</u> in the presentation of this information before the people of the United States

of America (U.S.A.), the World, and specifically the President of the U.S.A. without any compensation to the author. All submissions including this timeline bibliography can be obtained under the Freedom of Information Act (FOIA) by formally requesting a copy of NIAID Case #12276 from the FIOA Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

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87) 1995-01-04: Meyer HS: Gordon's Guide to the Surgical Morbidity and Mortality Conference. JAMA 1995; 273(1): 86-87. https://jamanetwork.com/journals/jama/articleabstract/385539

> Gordon advocates inclusiveness and honesty about complications—"An untoward event contributing to morbidity or mortality is a complication whether it is expected, anticipated, or not," and no type is exempt from presentation. He asserts that the familiarity a trainee gains at the M and M meeting with complications and their management is crucial to professional surgical development. He wishes training programs would resurrect the surgical notebook and the complications notebook, and the departments would devote real resources to M and M, including hiring an M and M secretary. ...

- 88) 1995-11 Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration: Guidance for Industry, Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Charaterized, Therapeutic, Biotechnology-derived Products. https://www.fda.gov/media/72057/download
- 89) 1996 Internet Archive: About the Internet Archive—a 501 (c)(3) non-profit building a digital library of Internet sites and other cultural artifacts in digital form. 300 Funston Ave, San Francisco, CA 94118 https://archive.org/ (Throughout this bibliography, the Wayback Machine of the Internet Archive has been used to identify earlier overwritten documents within the same URL.). https://archive.org/web/
- 90) 1996 Thall PF, Simon RM, Estey EH: New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.989.470&rep=rep1&type=pdf
- 91) 1996-08-30 Fauci AS: Letter to C.Everett Koop on his 80th birthday. https://profiles.nlm.nih.gov/spotlight/qq/catalog/nlm:nlmuid-101584930X417-doc
 - ... When people heard that I was a close friend of yours, they often asked me what it was like to know you and how impressed they were that you were a very unpredictable individual. I responded very confidently that, in fact contrary to their impressions, you were one of most predictable individuals that I had ever met. All one had to do was be insightful enough to figure out what the correct approach would be under unusually trying circumstances. Once you have that figured out, then Chick Koop is the most predictable person in the world because he always seems to do what is the most correct, honorable, and appropriate thing for the health of the Nation. This is your legacy and it is something for which you should be truly proud.

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- 92) 1997 Shuster E: Fifty years later: The significance of the Nuremberg Code. N Engl J Med 1997; 337 (20): 1436-1440. https://www.nejm.org/doi/pdf/10.1056/NEJM199711133372006?articleTools=true
- 93) 1997 Raffensburger J: Cook County Hospital. Encyclopedia of Chicago Cook County Hospital; The Old Lady on Harrison Street: Cook County Hospital, 1833-1995. Raffensburger JG, Boshes, eds. International Healthcare Ethics, vol 3, 1997. http://www.encyclopedia.chicagohistory.org/pages/336.html
- 94) 1997 Fisher JT: Dr. America. The Lives of Thomas A. Dooley 1927 1961. Amherst: University of Massachusetts Press, 1997. While Thomas Dooley, M.D. will always be a controversial, self-proclaimed, self-promoting figure in American history, his founding of his more than 20 clinics (MEDICO) in Southeast Asia after the conclusion of the French Indochina war was acclaimed at the time and their concept would be foundational in the establishment of Medecins Sans Frontieres (Doctors without borders). https://muse.jhu.edu/article/4109
- 95) 1997 Foley, John S.J. Peace Prayer. https://songstranslation.com/john-foley/peace-prayer/ https://www.youtube.com/watch?v=4vVlCXJt0Y4

Lyrics: Beautiful adaptation of the Prayer of Saint Francis of Assisi Peace Prayer --Music and Lyric John Foley, SJ

> 1... Lord make me a means of Your Peace Where there's hatred grown Let me sow Your love Where there's injury Lord Let forgiveness be my sword Lord make me a means of Your Peace 2... Lord make me a means of Your Peace When there's sadness here Let me sow Your joy When the darkness nears May Your light dispel our fears Lord make me a means of Your Peace 3... Lord grant me to seek and to share Less to be consoled Than to help console Less be understood Than to understand Your good Lord make me a means of Your Peace 4... Lord grant me to seek and to share To forgive in thee You've forgiven me For to die in thee

----- May 30, 2022 -----

Is eternal life to me Lord make me a means of Your Peace

- **96)** 1997-05-16 Clinton WJ: Remarks by the President in apology for study done in Tuskegee. THE WHITE HOUSE, Office of the Press Secretary. https://clintonwhitehouse4.archives.gov/New/Remarks/Fri/19970516-898.html
- 97) 1997-10-21 Cohen JJ: Statement of the AAMC on DHHS Inspector General "PATH" audits presented to the Subcommittee on Labor, Health and Human Services, Education and Related Agencies of the Committee on Appropriations, United States Senate. https://www.aamc.org/media/15286/download?attachment
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Abstract

The proposed practice of "evidence-based medicine," which calls for careful clinical judgment in evaluating the "best available evidence," should be differentiated from the special collection of data regarded as suitable evidence. Although the proposed practice does not seem new, the new collection of "best available" information has major constraints for the care of individual patients.

Derived almost exclusively from randomized trials and meta-analyses, the data do not include many types of treatments or patients seen in clinical practice; and the results show comparative efficacy of treatment for an "average" randomized patient, not for pertinent subgroups formed by such cogent clinical features as severity of symptoms, illness, co-morbidity, and other clinical nuances. The intention-to-treat analyses do not reflect important post-randomization events leading to altered treatment; and the results seldom provide suitable background data when therapy is given prophylactically rather than remedially, or when therapeutic advantages are equivocal. Randomized trial information is also seldom available for issues in etiology, diagnosis, and prognosis, and for clinical decisions that depend on pathophysiologic changes, psychosocial factors and support, personal preferences of patients, and strategies for giving comfort and reassurance.

The laudable goal of making clinical decisions based on evidence can be impaired by the restricted quality and scope of what is collected as "best available evidence." The authoritative aura given to the collection, however, may lead to major abuses that produce inappropriate guidelines or doctrinaire dogmas for clinical practice.

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- 101) 1998-08-12 36 U.S. Code 302 National motto: "In God we trust" is the national motto. PL-105-225, Aug. 12, 1998, 112 Stat. 1263; PL 107-293, 3(a), Nov 13, 2002, 116 Stat 2060. https://www.law.cornell.edu/uscode/text/36/302
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On Sept. 24, 1959, Thomas L. Crull was flying a newly arrived U-2C, Article 360, on a local flight, heading back to Atsugi after setting an altitude record. As the U-2's fuel ran low, the airplane suffered a flameout–forcing Crull to make a dead-stick, wheels-up landing at the Fujisawa glider strip, 10 miles from Atsugi. Crull emerged unhurt, but his airplane overran the runway and slid onto the grass.

Letting the airplane simply sit there unguarded was not an option. A short time later several security personnel, apparently wearing loud Hawaiian shirts and packing large revolvers, showed up and began to order the growing crowd at gunpoint to stand away from the secret aircraft. The tactic proved counterproductive as it only led to extensive publicity about the crash landing. Eventually, the airplane would be packed off to the US, repaired, and returned to service with Det. B in Turkey.

From there, that airplane would make its final flight. It came on May 1, 1960, and its pilot was Francis Gary Powers. Powers was flying high over Sverdlovsk, USSR, when his U-2 came under attack by some 14 surface-to-air missiles. The U-2 broke apart, but Powers parachuted down safely and was captured, given a

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trial, and sentenced to 10 years in a labor camp. He was freed in 1962 in an exchange for the Soviet spy, Rudolf Abel.

- 2001-09-20 Emanuel EJ, Miller FG: The ethics of placebo-controlled trials A middle ground. N Engl J Med 2001; 345: 915-919. https://www.nejm.org/doi/pdf/10.1056/NEJM200109203451211?articleTools=true
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https://www.va.gov/oaa/1400 1hk Oct2001.doc returns the VA official website which states: Sorry – we can't find that page. Using the Wayback Machine, for 2004-10-28: http://web.archive.org/web/20041028182959/https://www.va.gov/oaa/1400 1hk Oct200 1.doc which states on pages 8 - 9:

(3) Level 3. The staff practitioner is immediately available in the facility – campus for direct resident supervision according to local policy as approved by the Network Academic Affiliations Officer. The service chief is responsible for periodically reviewing cases done under Level 3 supervision to ensure that such supervision is appropriate.

Using the Wayback Machine another version of the Level 3 Supervision (now Level D) is identified: In VHA Handbook of July 27, 2005 signed by Jonathan B. Perlin, M.D. https://web.archive.org/web/20051107072236/http:/www.va.gov:80/OAA/1400 1hk Jul (Recission of the previous version of May 3, 2004 which cannot be found): y27 05.doc 4. Level D: Attending in OR Suite, Immediately Available. The supervising practitioner is physically present in the operative or procedural suite and immediately available for resident supervision or consultation as needed.

Using the only other "hit" on the Wayback Machine of December 21, 2016, http://web.archive.org/web/20161221045318/http://www.va.gov/oaa/1400 1hk Oct2001. doc VHA 1400.1 has been removed completely and in its place is the website of the U.S. Department of Veterans Affairs which states: "Page Not Found." De facto, the U.S. DVA, VHA misdirected official government documentation which is tantamount to destruction of evidence used in the trial of Andrus v VA, U.S. Court of Appeals for the Federal Circuit, docket # 03-3162.

- 2001-11-17 FBI: History: Amerithrax or Anthrax Investigation. 117) https://www.fbi.gov/history/famous-cases/amerithrax-or-anthrax-investigation
- 2002 Kennedy C: Profiles in Courage for our time. Woodward, Bob: Gerald R. Ford. New York: Hyperion, 2002. Pages 293-318. https://www.jfklibrary.org/about-us/news-andpress/press-releases/profiles-in-courage-for-our-time

Each of these men displayed a rare form of courage, sacrificing their own future, and that of their families, to do what they believed was right for the country. Their example comes down to us

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across the years, their stories are part of our history, and their spirt lives on. The John F. Kennedy Profile in Courage Award is presented annually to an elected official who carries on this tradition. When we created the award in 1990, some doubted we would be able to find politicians worthy of the honor. They were wrong. This book tells the stories of men and women at all levels of government, in all parts of our country, across the political spectrum, who have all stood fast for the ideals of America.

- 119) 2002 Eye witness to history: "Julius Caesar Crosses the Rubicon, 49 BC," EyeWitness to History. http://www.eyewitnesstohistory.com/caesar.htm
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- 127) 2003-03-03 Andrus CH: Andrus v VA. U.S. Court of Appeals, Federal Circuit. Case 03-3162. Oral arguments, March 3, 2004. The U.S. Court of Appeals, Federal Circuit's ruling in the case of Andrus v. VA was to fail to rule, *per curiam*. https://dockets.justia.com/docket/circuit-courts/cafc/03-3162

Andrus CH: To Care for Him Who Shall Have Borne the Battle, And for his Widow, and his Orphan—*A. Lincoln*. Registered in the Copyright Office of the U.S. Library of Congress, USA, April 5, 2004, ©TXu1-173-542, (Revised with cover letter, table of contents, and correspondence with the Office of the Counsel to the President: August 24, 2004, ©TXu1-196-220). A compilation of documents related to U.S. Court of Appeals for the Federal Circuit Case 03-3162 *Andrus v. VA*, VA OIG Inspector General Reports regarding VHA Part-Time Physician Time and Attendance and alleged inappropriate transfers of VA patients, and correspondence with the Office of the Counsel to the President. [Was submitted and has been included in the unpublished BioEthics collection of the Joseph and Rose Kennedy Institute of Ethics, Georgetown University, National Reference Center for Bioethics Literature supported by the U.S. National Library of Medicine. Notified on Sept. 13, 2004 that the title and table of contents of this manuscript are to be added to the library's "ETHX on the Web" at http://bioethics.georgetown.edu in September/October, 2004]

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From slide 10:

The coefficient of determination (r²) was 0.77 which indicates 77% of the variance of O/E ratios was attributable to the % of Attending Surgeons presence (and 23% was not)

On the next day, May 8, 2003, Richard Griffin, Inspector General, U.S. Department of Veterans Affairs testified before the Veterans Affairs Committee of the U.S. House of Representatives regarding "efforts to identify and eliminate fraud, waste, abuse, and mismanagement in programs administered by the Department of Veterans Affairs." His testimony was a summary of a previous month's report from the Office of Inspector General entitled: *Audit of Veterans Health Administration's part-time physician time and attendance*. The audit which was discussed in the previous reference.

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132) 2003-05-12 Huang Y: The SARS epidemic and its aftermath in China: A political Perspective. Institute of Medicine (US) Forum on Microbial Threats; Knobler S, Mahmoud A, Lemon S, *et al*, editors. Washington (DC): National Academies Press (US); 2004. https://www.ncbi.nlm.nih.gov/books/NBK92479/

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- 133) 2003-05-12 Takada A, Kawaoka: Antibody-dependent enhancement of viral infection: molecular mechanisms and *in vivo* implications. Rev Med Virol 2003; 13: 387-398. https://onlinelibrary.wiley.com/doi/full/10.1111/vox.12386
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- 136) 2003-11-10 Andrus CH: Ethical issues in "medicine" that touched our family. U.S. Copyright Office, TXu001145557 https://cocatalog.loc.gov/cgi-

bin/Pwebrecon.cgi?v1=2&ti=1,2&Search%5FArg=Andrus%20Charles%20H&Search%5FC ode=NALL&CNT=25&PID=711zUFrXvEu8UUeMe4Encu1iAYnRa&SEO=202203051817 42&SID=2

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- 2004-03-03 Andrus CH: Andrus v VA: Oral arguments regarding Resident Supervision in the OR before a three judge panel of the U.S. Court of Appeals for the Federal Circuit. Oral arguments, March 3, 2004. The U.S. Court of Appeals, Federal Circuit's ruling in the case of Andrus v. VA was to fail to rule, per curiam. https://dockets.justia.com/docket/circuit- courts/cafc/03-3162
- 139) 2004-03-16 Andrus CH: Correspondence from the US Office of Special Counsel in Andrus v. VA and allegations of obstruction of justice / compiled by Charles H. Andrus. U.S. Copyright Office, TXu001165703. https://cocatalog.loc.gov/cgibin/Pwebrecon.cgi?v1=11&ti=1,11&Search%5FArg=Andrus%20charles%20h&Search%5F Code=NALL&CNT=25&PID=y78dIAKyanVeyTb6Zs2tE9R4etD9sLF&SEQ=20210515161 739&SID=5
- 140) 2004-04-05 Andrus CH: To care for him who shall have borne the battle and for his widow and his orphan. U.S. Copyright Office, TXu001173542. https://cocatalog.loc.gov/cgibin/Pwebrecon.cgi?v1=12&ti=1,12&Search%5FArg=Andrus%20charles%20h&Search%5F Code=NALL&CNT=25&PID=XsOYHcY7XWAupNoXfDBOnuAs5Sn75IS&SEO=202105 15162652&SID=9
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- 143) 2004-04-08 Sawyer D: Fighting For Care, ABC News Primetime Live. https://vimeo.com/116428212 (now in the Internet Archive: https://web.archive.org/web/20211122005236/https://vimeo.com/116428212).

After OIG Inspector Griffin's testimony on May 8, 2003, ABC Primetime investigated for an entire year and on April 8, 2004, aired Fighting for Care narrated by Diane Sawyer. 2004-04-08 Sawyer D: Fighting For Care, ABC News Primetime Live. https://vimeo.com/116428212 (now in the Internet Archive: https://web.archive.org/web/20211122005236/https://vimeo.com/116428212) This episode was removed from the ABC Archives possibly because ABC to hidden cameras into the Cleveland and Waco VAMCs.

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2004 George Polk Award for "Television Reporting: Diane Sawyer and Robbie Gordon, ABC News Prime Time Live, for "Fighting for Care," which documented patient abuse and deplorable conditions in VA hospitals." (for investigative reporting excellence) https://liu.edu/polk-awards/past-winners#2004. When Tammy Shehari, the Associate Producer for the episode, spoke with me by phone in 3/2004, she asked me to estimate how many additional veterans had died due to unsupervised operations performed by Surgery Residents- I declined to guess because to do so would be wrong and a disservice to the Veteran patients and the men and women of Department of Veterans Affairs that do their duty faithfully for Veteran patients. (The interview ended shortly after my refusing to guess, and this was the only time ABC News spoke with me.)

Please note the reference above -- VHA USH, Robert Roswell, M.D. resigned three days prior to the airing of Fighting for Care. Fighting for Care contained within unauthorized hidden cameras in the Cleveland VAMC and the Waco VAMC. The VA spin was: ...Robert Roswell, who himself resigned in 2004 owing to problems with a multimillion-dollar computer system that the VHA had been testing in Florida. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690309/

https://web.archive.org/web/20040409151345/http://abcnews.go.com/sections/Primetime/Living/ VA Hospitals 040408-1.html

(Somewhere between Sept 1, 2004 and October 9, 2004, Fighting for Care was take off ABC News' Website when one uses the internet archive.—Charles Andrus, M.D., 3-20-2022)

Recently, there have been new stories of misdiagnosis, disastrous management and deficient care at some of the nation's 162 facilities.

At a hospital near Cleveland, an ABCNEWS hidden-camera investigation found bathrooms filthy with what appeared to be human excrement. Supply cabinets were in disarray, with dirty linens from some patients mixed in with clean supplies, or left in hallways on gurneys.

At a neighboring facility, examining tables had dried blood and medications still on them. In several areas, open bio-hazardous waste cans were spilling over. Primetime obtained internal memos documenting that the equipment used to sterilize surgical instruments had broken down — causing surgical delays and possible infection risks.

With 130,000 young American men and women putting their lives at risk in Iraq today, these conditions are particularly relevant. While current soldiers are treated in military hospitals, when they leave the service and need treatment, many will seek care at Veterans Affairs (as the Veterans Administration is now known)

"Once you come back to be a veteran, it's like a black hole, you know — nothing," former Army Sqt. Vannessa Turner told ABCNEWS.

Turner was stricken with a mysterious illness while on duty in Iraq this past year. She retired from the military on medical grounds, and when she reported to a VA hospital for treatment, doctors scheduled her for an appointment six months later.

Not a Point of Pride

Veterans who responded to a survey by the American Legion in 2003 said it took an average of seven months to get a first appointment at a VA hospital. In some hospitals, patients have waited as long as two years. In 1999, Jack Christensen, a former army sergeant who served in the Korean War, was admitted to the VA hospital in Temple, Texas, with pneumonia, and ended up staying three years.

Christensen's wife, Pat, says the attitude of some of the practical nurses was shocking. Some of the patients were forced to beg for food and water, she says. Instead of helping her husband go to the bathroom, she said, "they would put a towel under his hips and tell him to use the towel."

Pat Christensen said her husband's condition worsened over several months — so badly that at one point he developed horrific bedsores and dangerous infections, and she says his doctors said they would have to amputate his legs.

Pat moved her husband to a private facility, where his infection healed and he underwent extensive physical therapy. She sued the VA, and then used the money to pay for private care for her husband. The VA denied liability but paid a settlement.

Dr. Jonathan Perlin, the deputy undersecretary for health, said the VA system has sophisticated quality control. But when he was shown ABCNEWS' hidden-camera video of hallways and supply closets in disarray, he said, "This is something we're not proud of."

Fundamental Problems

Critics have long charged that the VA system puts patients on a kind of assembly line, passing them from doctor to doctor.

There's also criticism of how the VA uses residents — doctors still training and not certified in their specialties.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

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Terry Soles served in the Navy during the Vietnam War. His wife, Denise, says he was one casualty of this practice. In 1998, he went to the VA hospital in Cleveland complaining of pain and diarrhea, and doctors removed small cancerous growths from his stomach and esophagus.

But as his symptoms persisted over the next two years, his wife says the VA gave him painful tests and repeatedly lost the results. His wife says Soles was seen by a parade of constantly rotating resident doctors, and there was little consistency in his care.

Once, Soles was prepped for surgery but before the operation the doctors who were present couldn't agree on what they were going to do, she said.

Before he got sick, the 6-foot Soles weighed more than 200 pounds. By the time his family finally decided to take him to a private hospital, he weighed 80 pounds. Some VA doctors thought his problem was psychosomatic.

When he could no longer recognize his own son, Soles was rushed to a private hospital. There, Soles learned he was "a total mass of cancer from his trachea to his renal bowel. And that there was nothing that could be done," his wife says. Terry Soles died three days later.

The VA's Perlin said the Soles story was tragic, but added: "However, that is not the experience of most of the veterans who come to us for care. ... We take care of 7 million veterans. While the majority of care is good, in a big system, bad things happen."

Whose Fault?

Critics charge that one of the big problems facing the VA is that too much money goes toward administration, at the cost of nursing and patient care.

Dean Billik, the former director of the VA in Charleston, S.C., is brought up as an example.

In 1996, he was denounced for allegedly spending about \$200,000 in taxpayer money to redecorate his office; \$1.5 million to renovate a nursing home unit that stayed empty for two years; and tens of thousands of dollars for a fish tank in the lobby — while there were budget shortfalls and staff cutbacks were contemplated. Congress heard testimony claiming Billik was "blatant in his mismanagement," and an inspector general's report

confirmed several of the numerous allegations against him. But after everything was brought to light, Billik still got a bigger job: He was put in charge of the third-largest

hospital system in the VA, encompassing eight cities, 295 acres of land and 83 buildings. And his salary immediately jumped about \$15,000. Primetime obtained budget information on the central Texas VA system for Billik's six-year tenure at the top. It

confirms that Billik cut spending \$2 million for the people in direct patient care — nurses aides and practical

Other documents obtained by Primetime show that \$129 million was spent on construction at three of six facilities in Temple, Texas.

One source says Billik spent \$1.8 million renovating a building at Temple for his own offices — after it had been renovated for patient care.

Furthermore, Nancy Kelsey, who was a nurse at one of the Temple facilities under Billik's supervision, says the way some of the staff treated patients was alarming. She says IVs ran out, patients were neglected and dressings weren't changed.

Melba Bell, whose husband, Ed, served in Korea, said the staff was often idle and it would often take hours to get help. Other families said that if patients or their families persisted in asking for help, some of the staff retaliated.

At one point, Bell's infection got so bad that the hospital used maggots to try to eat away the decay. That's not unusual treatment, but what happened afterward was.

"The dressing that they had on there was real poorly done," said Bell's granddaughter, Chesney Shirmer. "Some of the maggots got out and they were in the bed with him, you know? He could feel them in the bed." Ed Bell died of gangrene in the VA hospital in 2002.

One More Problem

When confronted with these details, Perlin said he shared the outrage and promised to look into fixing these things.

But there is one more problem. Many whistle-blowers and critics say if you try to expose the truth, VA managers don't want to hear it.

Charles Steinert, who worked for Billik in Charleston, says he felt pressure to leave after he complained about some of the building projects and how he was being treated by supervisors.

Nurse Melissa Craven, who also worked at the Charleston VA, says she suffered retribution for two years after she spoke out about some of her supervisors.

Perlin said it is easy for patients and their loved ones to lodge complaints about VA care. "That's important to us, because if there are concerns, we want to address them," he said.

But many patients and their loved ones told ABCNEWS that wasn't their experience — and even worse, many of the families are afraid to speak out.

"They're afraid to say what really goes on, because they're afraid any little benefits that they have are going to be taken away from them," said Denise Soles.

Improvement Efforts

The day after Primetime presented its findings to the VA's Perlin, he ordered inspections of the facilities Primetime investigated.

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They found a number of problems at the Temple, Texas, VA, including poor hygiene, insufficient staffing and low satisfaction among patients and their families.

The VA announced it would bring in new supervisors, reassign some personnel, train others, and begin recruiting additional staff.

Inspectors who went to the VA in Cleveland said it was in good condition. However, after their visit, *Primetime* received phone calls from several sources saying that the hospital had advance warning of the so-called surprise inspection.

And to those patients who accuse the VA of assembly-line care — that patients go through a succession of doctors — a public relations officer for the VA said it tries to ensure continuity of care, but that may not always be possible.

As for Dean Billik, he has now retired. In a phone conversation on Wednesday, he said he disagreed with the VA inspectors, saying their report was "an opinion."

Billik said he relied on his staff to supervise nursing and recommend budgets, and if he had renovated some buildings that then were closed it was because he didn't possess 20/20 hindsight and made the best decisions at the time

Rep. Ted Strickland, a member of the House Veterans Affairs Committee, called for the White House and Congress to approve enough money to ensure that veterans get the care they deserve.

It's a "situation that's crying out for change," the Ohio Democrat said after viewing *Primetime's* tapes. Veterans and their families agree they deserve better. "They were good enough to go fight for their country," said Melba Bell. "They deserve to have the best treatment that they could get."

Denise Soles says that before her husband died he asked just one thing of her: to speak out.

She said Terry Soles told her, "If we can help one other veteran from going through the hell ... That's what we have to do."

Some Internet resources for veterans: Glreports, http://www.gireports.com; Iraq War Veterans Organization, http://www.iraqwarveterans.org; American Legion, http://www.legion.org; National Gulf War Resource Center, http://www.ngwrc.org

- 144) 2004-05-15 Christian MD, Poutanen SM, Loutfy MR, Muller MP, Low DE: Severe acute respiratory syndrome. Emerging Infections, CID 2004 May 15; 38: 1420 1427. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7107873/pdf/38-10-1420.pdf
- 145) 2004-05-03 Perlin JB: Resident Supervision.

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- 146) 2004-08-24 Andrus CH: To care for him who shall have borne the battle, and for his widow, and his orphan. U.S. Copyright Office, TXu001196220.

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147) 2004-09-16 Andrus CH: "Primum non nocere" and practicing ethics in medicine in this era of "the bottom line." U.S. Copyright Office, TXu001203831.

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148) 2004-10-07 Andrus CH: Rationing of medical care and the election of 2004. U.S. Copyright Office, TXu001192071. https://cocatalog.loc.gov/cgi-

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bin/Pwebrecon.cgi?v1=8&ti=1,8&Search%5FArg=Andrus%20charles%20h&Search%5FCo de=NALL&CNT=25&PID=4iZ1dm184qpLAbM4gtkZ6Lpi-K68hK&SEO=20210515160704&SID=3

Rationing of Medical Care and the Election of 2004

Summer 1999: VA OIG Combine Assessment Program; https://www.va.gov/oig/cap/99-00173-18.pdf

Dr. Thomas Garthwaite, VHA Undersecretary for Health, met at Dr. Garthwaite's request with Dr. Andrus in Atlanta, GA at the AVAS on April 8 & 9, 2001. Three days later after having met with Dr. Andrus, Dr. Garthwaite announced his resignation (but would stay on until January 2002 as the USH) and the official published reason for his resignation was:

> But Thomas Garthwaite, who had been Kizer's deputy undersecretary, maintained the momentum of the reforms during his tenure as (initially acting) undersecretary between 1999 and 2002. Garthwaite resigned over disagreements about policy direction with Anthony Principi, the first VA secretary appointed by the Bush administration (page 22)

Oliver A: The Veterans Health Administration: An American Success Story? The Milbank Quarterly. 2007 Mar; 85(1): 5-35. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690309/

It seemed as though a conjuncture of events very different from those that had opened the window for reform were conspiring against Kizer's leadership. To place Kizer's tenure in context, no undersecretary for health has ever been reconfirmed by the Senate for a second term, and Kizer is the only undersecretary ever to have been renominated by the White House, which indicates that he did still have the support of some senior politicians. Nonetheless, at the end of the nine-month extension of his contract, he resigned.

Leadership that commands great respect is probably quite rare in any large health care organization, and Kizer's departure could have been highly detrimental to the VHA. But Thomas Garthwaite, who had been Kizer's deputy undersecretary, maintained the momentum of the reforms during his tenure as (initially acting) undersecretary between 1999 and 2002. Garthwaite resigned over disagreements about policy direction with Anthony Principi, the first VA secretary appointed by the Bush

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administration, and was replaced by Robert Roswell, who himself resigned in 2004 owing to problems with a multimillion-dollar computer system that the VHA had been testing in Florida. From then until August 2006, Jonathan Perlin served as undersecretary. Even though it is inevitable that some staff will be dissatisfied with personal leadership styles and no undersecretary will be universally admired, my impression from those with whom I corresponded and interviewed is that the VHA has had at least three able leaders (i.e., Kizer, Garthwaite, and Perlin)

Veterans Health Administration: American Success Story? 23 since the mid-1990s and that their impact on morale and performance, albeit impossible to isolate and quantify, is likely to have been positive.

- 2004-11-30 Peiris JSM, Guan Y, Yeun KY: Severe acute respiratory syndrome. Nature Medicine Supplement 2004 December; 10(12):S88 – S97. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7096017/pdf/41591 2004 Article BFnm11 43.pdf
- 2004-12-23 Cheng Y, Wong R, Soo YOY, Lee CK, Ng MHL, Chan P, Wong KC, Leung CB, Cheng G: Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005; 24: 44 – 46. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7088355/pdf/10096 2004 Article 1271.pdf
- 2005 Andrus CH: Chapter 3: The Dog Lab and Chapter 12-14: Discussion and Reflections. Dear Mr. President...to care for him who shall have borne the battle.... Unpublished work. Appendix H: Andrus
- 2005 Corazzini KN, Lekan-Rutledge D, Utley-smith Q, Piven ML, Colón-Emeric CS, Bailey D, Ammarell N, Anderson RA: "The Golden Rule": Only a starting for quality care. NIH Public Access Author Manuscript, *Director* 2005; 14(1): 255-293. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1636677/pdf/nihms-8340.pdf
- 153) 2005-04 Peel M: Human rights and medical ethics. J R Soc Med 2005 Apr; 98(4): 171-173. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1079446/pdf/00980171.pdf
- 154) 2005-08-20 Andrus CH: Correspondence regarding the manuscript Mortality outcomes and attending surgeon presence at the time of operation. U.S. Copyright Office, TXu001262126 https://cocatalog.loc.gov/cgibin/Pwebrecon.cgi?v1=5&ti=1,5&Search%5FArg=Andrus%20charles%20h&Search%5FCo de=NALL&CNT=25&PID=49mUgm0LoUN2xjhEZHaERAuUD2qzDv0&SEQ=202105151 62031&SID=6

⁻⁻⁻⁻⁻ May 30, 2022 -----This is a COVID-19 Timeline Bibliography for Educational Purposes <u>ONLY</u> in the presentation of this information before the people of the United States of America (U.S.A.) the World and precife all the Parist of States and precife all the Parist of States. of America (U.S.A.), the World, and specifically the President of the U.S.A. without any compensation to the author. All submissions including this timeline bibliography can be obtained under the Freedom of Information Act (FOIA) by formally requesting a copy of NIAID Case #12276 from the FIOA Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

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- 2005-11 Itani KMF, DePalma RG, Schifftner T, Sanders KM, Change BK, Henderson WG, Khuri SF: Surgical resident supervision in the operating room and outcomes of care in Veterans Affairs hospitals. Am J Surg 2005; 190 (5): 725-731. https://www.americanjournalofsurgery.com/article/S0002-9610(05)00638-0/fulltext

"Abstract Conclusions: Between 1998 and 2004, the level of resident supervision in the OR did not affect clinical outcomes adversely for surgical patients in the VA teaching hospitals. (page 725)"

Table 1 Levels of attending supervision in the operating room as defined throughout the years of study (page 726)

1998-2002 Level 3: attending not present, but available

2002-2004 Level 3: attending not present in OR suite, immediately available

Level D: attending in OR suite, immediately available 2004

The Abstract Conclusions of "not affect clinical outcomes adversely for surgical patients", were **CONTRADICTED** BY THE VA'S reported absolute criteria: Emergency case, 30-day mortality rate, and return to OR

Table 4 Intraoperative variables (page 729)

Intraoperative variables. Attend 3 (N = 39,577). All other cases (N = 571,083. P value Emergency case 12.84% (5,080) 6.79% (38,785). < .001

Table 5 Unadjusted postoperative outcomes (page 730)

Outcome	Attend 3 ($N = 39,577$)	All other cases $(N = 571,083)$	P value
30-day mortality rate	2.66% (1,054)	2.34% (13,387)	< .001
30-day morbidity rate.	8.27% (3,274)	10.47% (59,805)	< .001
Return to OR.	10.24% (4,052)	8.19% (46,755)	< .001

2005-12-02 Andrus CH: Addendum to correspondence regarding the manuscript: Mortality outcomes and attending surgeon presence at the time of operation. U.S. Copyright Office, TXu001274328 https://cocatalog.loc.gov/cgi-

bin/Pwebrecon.cgi?v1=4&ti=1,4&Search%5FArg=Andrus%20charles%20h&Search%5FCo de=NALL&CNT=25&PID=j6kpQfMyPdWq0VDjv-N11SdPUGFYx9f&SEO=20210515162248&SID=7

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The old adage in medicine, "see one, do one, teach one," has changed. It was thought to have served medicine, especially surgery, well over the last century of changes in medical care and medical education, especially when there was no specific or formalized medical training in this country. However, in the new era of American medical compliance (Health Insurance Portability and Accountability Act, patient safety concerns, and compliance oversight), from our various professional societies as well as at the state and federal levels, this adage needs to be looked at again and may actually have been detrimental to the patient and the physician's overall well-being.

The days are long gone of residents being unsupervised and teaching other residents on a daily basis. ...

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The past seven years have seen a great deal of turmoil in teaching hospitals across the country. Disruptive events in the teaching environment have included the PATH (Physicians at Teaching Hospitals) audits and the resulting expectation for documented faculty presence during procedures, and additional enhanced documentation requirements on faculty and residents. Both have affected the relationship between faculty and residents, and have had a significant impact on the operation of teaching services. A number of our teaching hospitals are safety net institutions, and they have felt tremendous financial pressure. As clinical burdens have increased, faculty time and energy for innovation has been limited. The majority of our teaching hospitals are feeling the burden of the growing uninsured population, the need to provide service to these patients and the escalating needs of the growing population of elderly in the United States. These and many other factors diverted the efforts of the educational community, and slowed the work of innovation in evaluation of physician competency.

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Size of SARS-CoV-2

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December of 2019, many infectious disease specialists, as well as researchers for almost every avenue of medicine, have been investigating how this virus spreads to and infects human beings, the wide range of severe health effects it can cause and ultimately what drugs will be able to effectively kill this virus safely.

In addition to mechanistic information, researchers have also evaluated the size and content characteristics of the SARS-CoV-2 particles. Upon analysis of negative-stained SARS-CoV-2

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articles by electron microscopy, different researchers have had varying results, but the diameter of the virus has been found to range between 50 nm to 140 nm.

In addition to measuring the spherical size of the virus particle, it has also been confirmed that the length of the size tumors surrounding the outermost surface of SARS-CoV-2 can vary in length from 9 to 12 nm.

Why does size matter?

Around the world, health officials have agreed that wearing masks can prevent the spread of the virus between individuals. While this may be true, certain masks are considered much more effective at minimizing the risk of exposure, particularly N95 masks.

Whilst N95 masks from different producers may have slightly different specifications, the protective capabilities offered by N95 masks are largely attributed to the masks' obligation to remove at least 95% of all particles with an average diameter of 300 nm or less.

The size of a virus particle largely determines how individuals can protect themselves and those around them from acquiring SARS-CoV-2. Knowing the size of a single virus particle can also allow researchers and healthcare providers to infer the amount of virus individuals are exposed to through different routes.

For example, respiratory droplets are typically 5-10 micrometers (μ m) in length; therefore, it can be inferred that an individual who ingests, inhales, or is otherwise exposed to SARS-CoV-2 positive respiratory droplets can be exposed to hundreds or thousands of virus particles which increases the probability of infection.

Respiratory droplets can be transmitted through coughing, sneezing, contact with contaminated surfaces, or even through inhaled aerosols; therefore, each individual must take adequate steps to reduce their exposure to these particles by wearing masks and practicing safe social distance measures.

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Alexander Pope, poet of the Enlightenment, lent a famous line from his 1711 treatise An Essay on Criticism to the US Institutes of Medicine's report on patient safety: To Err is Human. ¹ The remainder of the line, "to forgive divine," would have further reinforced the report's message. Those who made mistakes should neither be blamed nor punished, it argues, instead, to look at the system. ...

- ... Elsewhere in his essay, Pope stresses the many human factors that lead to bad outcomes: overconfidence, tunnel vision, bias, prejudice and inconsistency, among others, and exhorts us to combine "good nature and good sense" in our judgment. ...
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Many years ago, in the Basque country of Spain, there lived a prosperous and generous family who, after feeding family, retainers, and soldiers, had enough to feed even the wild animals. To commemorate this act of generosity, a carving of two wolves eating at a cauldron was placed over the lintel of the family's home in Loyola, Spain.

Many centuries later, St. Ignatius of Lovola would be born into this family and would go on to establish the Jesuit order and change the world. Today, we celebrate this act of generosity, which has become the heraldic shield of the Loyola family, the symbol of this University, and a fitting tribute to our donors, whose generosity makes your education possible at Loyola.

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"He was a real icon before he even became surgeon general," said Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases and a longtime friend and colleague of Koop.

Koop considered retiring after a trailblazing career that resulted in surgical techniques still used today to save tiny newborns. Yet being tapped to serve as surgeon general at age 64 excited Koop, who as he approached his 91st birthday, credited his longevity to both genetics and working in a field he adores.

"I've never had a job where I didn't like to get up in the morning and go to it, and that's, I think, unusual," he said from his office at the Koop Institute at Dartmouth. "I told that to a group of medical students a couple of years ago and they looked at me like I was out of my mind."

Known for his powerful speaking voice and trademark beard that have led some to describe him as resembling an Old Testament prophet, Koop likely was such an effective surgeon general because he truly cared about the people he was working to protect. And he doesn't mince words or tiptoe around what some might think of as political land mines.

"He's a completely transparent, honest, tell-it-like-it-is kind of person," said Fauci, once Koop's personal physician and a confidant at the time the surgeon general was working on his controversial AIDS report. "He's just not afraid of anybody."

"This is a man who, above all else, is willing to communicate his convictions with courage when it's the right thing to do," said Timothy Johnson, MD, MPH, medical editor for ABC News and coauthor with Koop of Let's Talk: An Honest Conversation on Critical Issues: Abortion, Euthanasia, AIDS, Health Care. "He's always willing to dialogue and listen to the other side. I think that's a great strength."

... Koop said. "I did a lot of things that I thought were public health, and that stood me in good stead for decisions I had to make. It wasn't nearly the leap that some people think it was or that you might think it is, to go from being a surgeon of individual patients who had a surgical problem to 347 million people, which is what the population was when I went to Washington."

Just before a group of public health luminaries headed to a dessert table to cap off Koop's 90th birthday celebration in Washington, DC, the guest of honor gave an impassioned speech about the need for health care reform. Echoed in a December 2006 Journal editorial, Koop outlined 3 core principles for reform: the fundamental right of all people to have the highest standard of health care, that disparities are "absolutely unacceptable" and at odds with the

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right to health, and that public, private, and health-related agencies need to make disease prevention and health treatment a priority.

Former Surgeon General Richard Carmona, who served from 2002 to 2006, said Koop brought the office "to a new standard" and was effective because he "stepped up and took risks and did the right thing." Koop said his success can be attributed to a combination of factors.

"I look back on those days, and some things I accomplished because I was naïve. Some things I accomplished because I was furious and I wasn't going to let that stand in my way," Koop said with a smile. "Other things I accomplished by what I call moral suasion . . . and by that I mean having an explanation for what you want to do that transmits the passion you feel for it, the rightness of what you want to do and why it is good for the recipients to have somebody advocate for them because nobody else will."

Those who know Koop well, including Johnson of ABC News, know that the man who hopes to be remembered as "the health conscience of the nation" will work as long as he's able to improve the public's health. "He studies. He knows what he's talking about," Johnson said from his office in New York. "He knows how to say things that will capture your attention."

1990-10-08 Koop, CE: Speech: 'Exasperation on both sides of the stethoscope' American College of Surgeons, San Francisco, CA, October 8,1990.

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THEREFORE, MY MESSAGE TO THE DOCTORS IN AMERICA IS: WHEN YOU ARE DEALING WITH A PATIENT YOU ARE REPRESENTIING ALL OF AMERICAN MEDICINE, YOU ARE REPRESENTING AMERICAN HEALTH CARE.

WE HAVE MUCH TO DO, BUT LET'S NOT LOSE OUR POSITIVE ENERGY.

THE MESSAGE WE HAVE TO SHARE WITH OURSELVES AND WITH THE AMERICAN PEOPLE IS A POSITIVE ONE. WE DON'T NEED THE PAST TENSE,...NOSTALGIA ABOUD THE GOOD OLD DAYS; NOR DO WE NEED SOME FUTURISTIC MANIFESTO PROMISING WHAT WE INTEND TO DO.

WE NEED CLEAR AND PERSISTENT AFFIRMATION OF THE MANY GOOD THINGS WE DO, DAY IN AND DAY OUT, TO MAKE OUR SYSTEM OF MEDICINE—ONCE WE TAKE THINGS IN HAND-POTENTIALLY THE BEST IN THE WORLD.

I HAVE NEVER REGRETED GOING INTO MEDICINE. I'D DO IT AGAIN TOMORROW. AND I TELL THAT TO ANY YOUNGSTERS WHO ARE CONSIDERING IT.

OURS IS A CALLING. IT IS NOT A BUSINESS. WE COULD HAVE MADE MONEY DOING OTHER THINGS

WE CHOOSE MEDICINE -SURGERY-BECAUSE IT COMBINED A QUESTF FOR KNOWLEDGE WITH A WAY TO SERVE, TO SAY LIVES, AND TO ALLEVIATE SUFFERING.

WE HAVE TO CONVINCE THE PUBLIC WE STILL MEAN IT; IF WE DO, WE'LL GET WHAT WE NEED TO DO THE JOB RIGHT.

I THINK I POSSESS A CERTAIN AMOUNT OF CREDIBILITY, BOTH WITH YOU AND THE GENERAL PUBLIC. I HOPE MY REMARKS TO YOU TODAY DID NOT COST ME SOME OF MY CREDIBILITY WITH SOME OF YOU BECAUSE YOU DON'T LIKE WHAT I SAID. I THINK YOU ALL KNOW THAT MEDICINE IN AMERICA IS IN DEEP TROUBLE, MAYBE AT A TRUE CROSSROADS.

IF YOU DON'T WANT TO SEE US TAKE THE ROAD TO CANADA, OR GREAT BRITAIN, SO SOMETHING NOW. WE MUST DO SOMETHING, SOMETHING TO REKINDLE THE LOVE OF OUR LPROFESSION, THE PRIDE IN LOFTY ETHICS, THE ENJOYMENT OF MEDICINE.

DON'T JUST WRING YOUR HANDS AND GRUMBLE BECAUSE "THEY" HAVEN'T DONE SOMETHING.

----- May 30, 2022 -----

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YOU ARE THEY.

https://profiles.nlm.nih.gov/spotlight/qq/feature/biographical-overview

..... Through his speeches, publications, and films Koop rose to prominence among antiabortion activists, and eventually came to the attention of newly-elected president and abortion foe Ronald Reagan, who nominated Koop as U.S. Surgeon General in March 1981. During eight months of controversy and congressional hearings, critics and supporters debated his stance on abortion as well as the question whether Koop, who had devoted his career to treating individual patients, was qualified to address the health needs of the nation as a whole. He was confirmed as U.S. Surgeon General in November 1981.

During his two terms as Surgeon General, Koop made himself the most prominent government spokesman on issues affecting the health of the American public, despite having little statutory authority and a small budget. He infused a renewed sense of confidence and purpose into the Commissioned Corps of the U.S. Public Health Service (PHS), a federal service of public health professionals that the Surgeon General commands and that had been suffering from low morale after the closing of PHS hospitals and the cut-back in personnel in the early 1980s. He examined medical ethics, health care costs, and the problem of the uninsured in a health care system that faced financial challenges at a time of inflation followed by recession in the early 1980s. ...

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While the website above the generalities, to submit FOIA request is somewhat complicated and the following disclaimer for the NIH—National Institutes of Health in part is: ...Please submit all requests through our online portal (link below) rather than mail, fax, or courier, to ensure timely logging of your requests....

First (1): https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/freedom-information-act-office/submitting-foia-requests

Next (2): click on the Submit a FOIA Request:

Submit a FOIA Request

Next (3): The following disclaimer will show up which after reading it, if one wishes to proceed, you should click on "I Accept":

You are about to access a United States Government computer system. This information system is provided for U.S. Government-authorized use only. Unauthorized or improper use of this system may result in disciplinary action, as well as civil and criminal penalties.

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- You have no reasonable expectation of privacy regarding any communication or data transiting or stored on this information system. At any time, and for any lawful Government purpose, the government may monitor, intercept, and search and seize any communication or data transiting or stored on this information system.
- Any communication or data transiting or stored on this information system may be disclosed or used for any lawful Government purpose.

No particular form is prescribed for making a FOIA request. You may submit a FOIA request using the NIH FOIA Request Portal or in any manner that conforms to the HHS FOIA regulations. http://www.hhs.gov/foia/statutes-and-resources/45cfr5/index.html

Privacy Act Statement

This Statement is provided pursuant to the Privacy Act of 1974 (5 U.S.C. § 552a): The information you are requested to provide in order to use the NIH FOIA Request Portal is authorized to be collected under the Freedom of Information Act (5 U.S.C. § 552). Completing the request portal fields is voluntary, but failing to provide any or all of the requested information may prevent HHS from creating a portal account for you, or may prevent HHS from processing your request. The principal purposes for which HHS will use the information that you provide in the NIH FOIA Request Portal are to create an account for you, and to track, process, and respond to requests that you submit to HHS through your account. The information you provide will be included in a Privacy Act system of records, and will be used and may be disclosed for the purposes and routine uses described and published in the following System of Records Notice (SORN): 09-90-0058 Tracking Records and Case Files for FOIA and Privacv Act Requests Appeals https://www.federalregister.gov/articles/2016/03/29/2016-07060/privacyact-of-1974-system-of-records-notice

https://www.congress.gov/114/bills/s337/BILLS-114s337enr.xml

https://www.justice.gov/oip/freedom-information-act-5-usc-552

All requests received after 5 pm Eastern Time, will be considered "received" on the next business day.

Next (4): You will then be electronically directed to: The NIH Website for submissions.

Next (5) When you actually submit the prose of your request, you should request:

NIAID Case #12276 NIH National Institute of Allergy and Infectious Diseases

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Which was opened on June 10, 2020 in which the correspondence stated: "...Due to his professional responsibilities, Dr. Fauci has asked me to respond on his behalf."

By:

Kara M. Harris, MPH
Section Chief for Controlled Correspondence and Public inquires
Legislative Affairs and Correspondence Management Branch
Office of Communications and Governmental Relations
National Institute of Allergy and Infectious Diseases
National Institutes of Health

After reviewing Dr. Fauci's *White House* slide show on Monoclonal Antibodies of August 24, 2021, 10:30 to 15:27 minutes on the URL, I called Ms. Harris's office on 8/30/2021 leaving a message requesting that Dr. Fauci call me. In a phone response to my phone call (my VA office phone number is: 314-652-4100 ext 54463), "Meg" who identified herself from Ms. Harris's office responding for their office stated that all the information I had submitted had been forwarded to the appropriate divisions. I then pleaded my case with "Meg" who patiently listened for about twenty minutes. Finally, when she stated she needed to go, she stated in her parting comments that she assured me that they still had all the information I had submitted in NIAID Case #12276. Thus, under FOIA, all in NIAID Case #12276 should be available to anyone properly requesting it under Federal Law.

[Please note Dr. Fauci's opening comments in his White House slide show: https://www.youtube.com/watch?v=AZNP05w2cxU

DR. FAUCI: Thank you very much, Dr. Walensky. I'd like to spend the next couple of minutes in addressing a much-underutilized intervention for COVID-19, and that is the use of monoclonal antibodies for the TREATMENT and PREVENTION of SARS-CoV-2 infection and COVID-19 disease.

Next slide.

For those not totally familiar with this, monoclonal antibody is an antibody that's produced by a single clone of B cells or a cell line, and consists of identical antibody molecules that can actually be produced in the in-vitro situation in unlimited quantities.

Next slide.

If you look at the virion on the upper-left part of the slide and you look up the blown-up spike protein — the red molecule on the right upper panel — when you talk about polyclonal antibodies, which result from infection or vaccination, it's a group of antibodies against every aspect of the spike protein, which is the good

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news. However, the concentration and the affinity of those antibodies can be markedly improved if you get a single cloned antibody — hence the word "monoclonal" — that's against the very specific part of the spike protein that can have a major effect in prevention and treatment. ...]

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Exploring the ACGME Core Competencies: Practice-based learning and improvement (Part 2 of 7) https://knowledgeplus.nejm.org/blog/practice-based-learning-and-improvement/

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Exploring the ACGME Core Competencies: Medical Knowledge (Part 5 of 7) https://knowledgeplus.nejm.org/blog/acgme-core-competencies-medical-knowledge/

Exploring the ACGME Core Competencies: Interpersonal and Communication Skills (Part 6 of 7) https://knowledgeplus.nejm.org/blog/acgme-core-competencies-interpersonal-and-communication-skills/

Exploring the ACGME Core Competencies: Professionalism (Part 7 of 7) https://knowledgeplus.nejm.org/blog/acgme-core-competencies-professionalism/

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In July 2020, Dr. Behrns was a General Surgeon of the Department of Surgery, Saint Louis University School of Medicine; co-Editor-in-Chief of *Surgery*; and was a fellow faculty member in General Surgery Division, Department of Surgery, Saint Louis University School of Medicine of Saint Louis University and shared the General Surgery outpatient offices with me on Friday mornings. Knowing that he had graduated from the Mayo Clinic Medical School and had been a Surgery resident and researcher at the Mayo Clinic in the 1990's, I requested of him that he contact Michael Joyner, M.D., the Principal Investigator for the Mayo Clinic / FDA Expanded Access program for COVID-19 Convalescent Plasma. Dr. Joyner responded with a brief e-mail response to Dr. Behrns:

Having a lot of trouble with USG.

By that time in July 2020, I had submitted to the offices of Dr. Fauci, Dr. Hahn, and President Trump multiple communications regarding *Passive Immunization treatment* with COVID-19 Convalescent Plasma which had been included in my submissions 1.) to the U.S.

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Copyright Office to be preserved for history in the Library of Congress and 2.) had been included in NIH NIAID case #12276:

> 1. Andrus CH: *Time*: The Crucial *Independent* Variable of the COVID-19 Pandemic, U.S. Copyright Office, Library of Congress, 2020-06-08, Txu002199029. https://web.archive.org/web/20210904014401/https://cocatalog.loc.gov/cgibin/Pwebrecon.cgi?v1=9&ti=1%2C9&Search Arg=Andrus+Charles+H&Sear ch Code=NALL&CNT=25&PID=DvTGOW Qvd foYxTFrVcdewL3ktMC wz&SEQ=20210425193720&SID=1

> 2. Andrus CH: The Mayo Clinic "Safety Update" should be classified as a completed Phase I trial of COVID-19 convalescent plasma. U.S. Copyright Office, 2020-07-22, TXu002214049. https://web.archive.org/web/20210904020833/https://cocatalog.loc.gov/cgibin/Pwebrecon.cgi?v1=6&ti=1%2C6&Search Arg=andrus+charles+h&Searc h Code=NALL&CNT=25&PID=cXfFuGrmHQvLVlLvfNNt7Yjwh73ImgQ &SEO=20210512081428&SID=1

Dear Mr. President, please note that all information I have submitted over the last two years to Dr. Fauci was directed by Dr. Fauci to be dealt with by:

> Kara M. Harris, MPH Section Chief for Controlled Correspondence and Public Inquires Legislative Affairs and Correspondence Management Branch Office of Communications and Governmental Relations National Institute of Allergy and Infectious Diseases National Institutes of Health

Per her letter of June 10, 2020, Ms. Harris assigned my correspondence with Dr. Fauci's office to NIAID Case #12276 and I have continued to submit my correspondence addressed with Dr. Fauci's office for the last two years labelled in the heading: NIAID Case#12276. After reviewing Dr. Fauci's White House slide show on Monoclonal Antibodies of August 24, 2021, 10:30 to 15:27 minutes on the URL, I called Ms. Harris's office on 8/30/2021 leaving a message requesting that Dr. Fauci call me. In a phone response to my phone call (my VA office phone number is: 314-652-4100 ext 54463), "Meg" who identified herself from Ms. Harris's office responding for their office stated that all the information I had submitted had been forwarded to the appropriate divisions. I then pleaded my case with "Meg" who patiently listened for about twenty minutes. Finally, when she stated she needed to go, she stated in her parting comments that she assured me that they still had all the information I had submitted in NIAID Case #12276. Thus, under the Freedom of

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Information Act (FOIA), all in NIAID Case #12276 should be available to anyone properly requesting it under Federal Law.

Mr. President, please excuse my digressing from Dr. Joyner's e-mail response to Dr. Behrns of: Having a lot of trouble with USG. Mr. President, could you please excuse the 'expletives' (E!) that I will include in my discussion that follows because over the course of the last two years the American people (and the World) have been misled, misinformed, and lied to (E!) regarding major issues of treatment of COVID0=19 by agencies of the Federal Government (e.g., FDA, NIH, CDC, PHS, VA, etc.), spokespersons of Organized / Academic Medicine (e.g.: The New England Journal of Medicine), and the Biological and Pharmaceutical industries assisted by B.A.R.D.A., other research agencies like DARPA, etc.

After Dr. Behrns voiced Dr. Joyner's e-mail response of "having a lot of trouble with *USG*", Dr. Behrns questioned me as to who was USG? My response was simple: USG is the United States Government; and Dr. Joyner was referring off-handedly to a nebulous but responsible/accountable **USG**. I then explained that the **USG** had so screwed up (E!) that "they" didn't know how to get out of the rabbit hole.

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- 2017-01-28 U.S. National Institutes of Health, U.S. Department of Health and Human Services: NIH policy on the dissemination of NIH-funded clinical trial information. Notice Number: NOT-OD-16-149, Release Date: September 16, 2016, Effective Date: January 18, 2017. https://grants.nih.gov/grants/guide/notice-files/not-od-16-149.html

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- The Red Cross begins National Blood Donor Service to collect blood for the U.S. military with Dr. Charles R. Drew, formerly of the Plasma for Britain program, as medical director.
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NIH, National Institutes of Health: Glossary of Common Terms. https://www.nih.gov/health-information/nih-clinical-research-trials-you/glossary-common-terms

260) 2018-01-29 STS Press Release: Keith S. Naunheim elected President of The Society of Thoracic Surgeons – Saint Louis University surgeon will focus on health care delivery and reimbursement. https://www.sts.org/sites/default/files/press-releases/President%20release Naunheim FINAL FMT.pdf

Over the years, in Dr. Naunheim's discussions of many articles in the literature, he has pointed out to the Saint Louis University students, residents, and faculty the always-possible inherent potential skewing of a statistical analysis by excluding a large number of individuals (e.g.: infected, cancer positive, non-control individuals, etc.) from a prospective Randomized Controlled Trials (RCT) until the decreasing denominator renders the RCT underpowered and useless. He has often referred to this as: "The Amazing Shrinking Denominator." The reference that follows entitled: Koehsen W: Lessons on how to lie with statistics – Timeless data literacy advice. https://towardsdatascience.com/lessons-from-how-to-lie-with-statistics-57060c0d2f19 is analogous to Dr. Naunheim's expression of "The Amazing Shrinking Denominator":

Scientists are usually limited to small samples by legitimate problems, but advertisers use small numbers of participants in their favor by conducting many tiny studies, one of which will produce a positive result. Humans are not great at adjusting for sample sizes when evaluating a study which in practice means we treat the results of a 1000 person trial the same as a 10 person trial. **This is known as "insensitivity to sample size" or "sample size neglect".**

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 https://www.cuimc.columbia.edu/news/rhogam-50-columbia-drug-still-saving-lives-newborns
- 262) 2018-03-01 Yan F, Thall PF, Lu KH, Gilbert MR, Yuan Y: Phase I-II clinical trial design: a state-of-the-art paradigm for dose finding. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5888967/pdf/mdx795.pdf
- **263)** 2018-03-05 FDA: Vaccinia Immune Globulin Intravenous. https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/vaccinia-immune-globulin-intravenous-human

VIGI (Human) Package insert: https://www.fda.gov/media/77004/download

VIGIV (Human) Package insert: https://www.fda.gov/media/78174/download

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In the NEJM Managing Editor's interview of Dr. Fauci regarding this publication, Dr. Fauci laid out the exact same discussion and advocacy for early treatment of novel viruses with monoclonal antibodies 8 months before SARS-CoV-2 was even seen or identified on this earth!: Morrissey S, Fauci A: Interview with Dr. Anthony Fauci on the use of monoclonal antibodies in the context of emerging infectious diseases. Supplement to the N Engl J Med 2018; 378: 1469-1472. (Mr. President, please listen to this five minute interview after reviewing Dr. Fauci's youtube slide presentation and discussion of the August 24, 2021 White House briefing (minutes 10:30 to 15:25): https://www.youtube.com/watch?v=AZNP05w2cxU.

The hyperlink for the 2018 NEJM Morrissey interview of Dr. Fauci is: https://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMdo00246 5&aid=10.1056%2FNEJMp1802256&area=

Dr. Morrissey:

Although there is a long history of plasma derived treatments for several pathogens, only a handful of antibody therapies have been licensed for infectious diseases. But recent advances in the development of monoclonal antibodies could have important implications for our response to infectious disease outbreaks. I'm Stephen Morrissey, Managing Editor of the New England Journal of Medicine, and I am talking with Anthony Fauci, Director of the National Institute of Allergy and Infectious diseases. Dr. Fauci has coauthored a prospective article about the promise of monoclonal antibodies for rapid intervention during infectious disease outbreaks. Dr. Fauci: What are the primary benefits of using monoclonal antibodies for prevention and treatment infectious diseases? What advantages do they have over current approaches?

Dr. Fauci:

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Well, one of the things that got us to be very interested in that is just that potential advantage. Namely, that when you have to respond, for example, to an unexpected outbreak of an infectious disease, one of the major tools against that to control it or hopefully eliminate it is development of a safe and effective vaccine. The problem with that is that the time that it takes, even when you put it on a rapid pace, the time that it takes to get a vaccine that you show to be safe and effective often falls behind and lags dramatically behind the actual outbreak itself. Whereas if you can with our techniques that we have right now which of greatly improved over the past several years to isolate and develop monoclonal antibody specific to the agent in question--you can use it much more rapidly. Obviously there's the issue of being able to scale up, but you get a monoclonal antibody in hand soon after you're confronted with an outbreak has a major advantage over the long time-honored but nonetheless rather drawn out process of developing a vaccine.

Dr. Morrissey:

You write in your article that several antibody therapies have been licensed for infectious diseases. What have researchers learned from the development of those therapies and for more recent attempts to create monoclonal antibodies against—say-- Ebola or Zika?

Dr. Fauci:

Well, for example, a classic monoclonal antibody for prophylaxis against Respiratory Syncytial Virus has been developed with considerable success. We began thinking very intensively about this just literally over the past few years when we in rapid succession had to confront both the Ebola outbreak followed by the Zika outbreak. And it became very clear that during the Ebola outbreak that there were monoclonal antibodies in the form of ZMapp that was able to actually have an impact even though we did not have the opportunity of doing a very large clinical trial. We did show that there was clearly a tendency towards a benefit of this cocktail of three mouse human chimeric antibodies against Ebola, that we felt that this particular approach if perfected both in the development and scale-up of these antibodies might have an important role in future outbreaks. So, we're thinking that this is going to be something, and including for example influenza, so there have been now a couple of monoclonal antibodies that have been made against influenza. And when you think in terms of a threat of a pandemic influenza and you would want to get an antibody that would be effective in neutralizing a brand new virus well before the time it takes to develop the vaccine, here again is something that we're going to be pursuing and are pursuing at the present time.

So how do you envision that process of developing new antibody therapies during an outbreak?

Dr. Fauci:

There a couple of ways of doing that. Probably the easiest way, because the technology now is so sophisticated, is to get an individual who has been infected with whatever pathogen is the one behind the outbreak. And because of the ability now to clone the B cells from the B cell repertoire and essentially fish out—and, truly metaphorically fishing-out the right B cell clones that have the specificity that you are thinking about and wanting to develop and immediately get those to be cloned, sequenced, and then the development of a high through-put process to give you monoclonal antibodies. That's something that was unheard of years ago—literally unheard of where you can actually probe and interrogate the B cell repertoire and the B cell lineage of a person who has recovered from the infection in question; and use those B cells as the source of the monoclonal antibody in question. And that's something that could be done immediately,

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and from the standpoint of the process of it, to be done very rapidly. So you can envision an outbreak where you have right-away, the sentinel people you have clearly getting sick from the pathogen you have in question and as they recover you just draw some blood from them and you can pull out with the techniques we have a variety of B cell clones that have various specificities and then you can test in vitro what is the best, what has the highest affinity, what is the most specific, what are the epitopes involved, and then start using them for both diagnosis, prophylaxis, and for treatment.

Dr. Morrissey

You talk in your article about the current high cost of production and complexity of administration of these monoclonal antibodies. So how great a limitation is that and do you foresee a time when those issues will be less of a barrier than they are now?

Dr. Fauci:

Well, that's a great question, and I'd have to answer totally, honestly—that it is a barrier that is substantial right now at present. But as we've done with so many other things that we've been able, we in the field, not me personally, but we in the field have been able to develop over years--is that once you get the first step namely the specificity, the effectiveness of a particular antibody, then you work on the development of scale-up. But the idea of scaling up at a reasonable cost where these antibodies can be used widely is a challenge. But I do believe that as we get better and better at it as we have with other technologies that have started off to be very cumbersome and very expensive, I believe over time when there is accelerated interest in this approach which I believe there will be that we will be able to overcome that barrier of the ability to produce at a high degree.

Dr. Morrissey:

In your article, you describe three indications for monoclonal antibodies: the treatment of infected individuals, targeted prophylaxis to protect high-risk individuals, and targeted prophylaxis to interrupt transmission in populations at average risk. So which of these strategies do you think has the most potential to halt the spread of an epidemic?

Dr. Fauci:

Well, clearly if you are talking about halting the spread of an epidemic, the last two that you mentioned because the first one is the treatment of an infected individual. Now obviously you can say well treatment will turn out to be prevention because if you treat a particular person they may not transmit it to another; but I think the much more efficient way of preventing the expansion of an outbreak is the targeted prophylaxis either directly at high risk individuals or even at a population level to prophylaxis and interrupt transmission in people who are at average risk and that is really what we talk about in interrupting the chain of transmission. So, if you have an influenza outbreak, you may be able to use this as prophylaxis before you get a vaccine that is available to essentially have a more population-based prevention. So, I believe the high risk individuals that are targeted for prophylaxis is going to be a very important way to interrupt certain outbreaks regardless of what the source of that outbreak is.

Dr. Morrissev:

Finally, what will it take to increase our interest in our investment in the use of monoclonal antibodies for infectious diseases? What, for example, is NIAID doing?

Dr. Fauci:

Let me answer your question broadly, then I will get back to the specific of what we are doing. Really nothing succeeds like success as they say. Once you start demonstrating the effectiveness of this approach in different outbreaks—and we have seen inklings of

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this with the ZMapp approach to Ebola with some of the monoclonal antibodies—all-beit in the animal models with Zika, they worked very well in the animal models to prevent the transmission of the virus to a fetus in an animal model; and thus prevented the congenital defects in this animal model. I believe that when we get to the point of testing it in humans, under these circumstances, we will see similar success. So, that is what I mean by nothing succeeds like success once you have a few examples of successful application of this particular approach. You are going to get a lot more interest in it. What we at NIH are doing is what we do most of the time is these types of approaches; and that is, to do the basic and clinical research to get this developmental process to be quick and to be effective. We done that and it ranges all the way from the fundamental basic research on B cell lineage--that really led to the ability to develop monoclonal antibodies at a high degrees of specificity and the high degree of ability to neutralize whatever a particular pathogen you have in question. So, the NIH 's job will be what we have been doing all a long, is the fundamental basis to give clinical research leading to the application of these types of interventions.

Dr. Morrissey: Thank you, Dr. Fauci.

- 269) 2018-05-08 NIH, NIAID: H. Clifford Lane, M.D., NIAID Deputy Director, Clinical Research and Special Projects, Director, Division of Clinical Research. https://www.niaid.nih.gov/about/h-clifford-lane-md-bio
- 270) 2018-05-30 President Trump signed into law PL-115-176: Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina, the RIGHT TO TRY ACT OF 2017. https://www.govinfo.gov/content/pkg/PLAW-115publ176/pdf/PLAW-115publ176.pdf

What is on the following pages is a copy of Public Law 115-176. As is stated in SEC. 561 B. INVESTIGATIONAL DRUGS FOR USE BY ELIGIBLE PATIENTS, (a), (2)the term 'eligible investigational drug' means an investigational drug (as such term is used in section 561)—(A) for which a Phase 1 clinical trial has been completed; (B) that has not been approved or licensed for any use under section 505 of this Act or section 351 of the Public Health Service Act; Throughout the COVID-19 Pandemic over the last 16 months, the FDA and the NIH in all announcements, policy statements, etc. have equated safety with efficacy—WHICH IS A MISINTERPRETATION OF PL-115-176. Distinctly by FDA and NIH definitions, Phase 1 clinical trials are SAFETY clinical trials while Phase 2 and 3 clinical trials are EFFICACY clinical trials. In short, when a Phase 1 clinical trial is deemed "Completed" by the FDA, the Investigational drug or biologic should be available to all individuals who have contracted a potentially terminal disease like COVID-19 under PL-115-176 until the FDA designates a New Drug Authorization number making the drug or biologic noninvestigational and thus available to all. By the FDA NOT "officially" declaring "Completed" Phase 1 clinical trials for any of the *Passive Immunization agents* and by RADM Denise Hinton, R.N., M.S. issuing Emergency Use Authorizations (EUA) for all Passive Immunization agents, all Passive Immunization agents are ALL INVESTIGATIONAL at present time.

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Public Law 115–176 115th Congress

An Act

May 30, 2018 [S. 204]

To authorize the use of unapproved medical products by patients diagnosed with a terminal illness in accordance with State law, and for other purposes

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017. 21 USC 301 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017".

SEC. 2. USE OF UNAPPROVED INVESTIGATIONAL DRUGS BY PATIENTS DIAGNOSED WITH A TERMINAL ILLNESS.

(a) IN GENERAL.—Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by inserting after section 561A (21 U.S.C. 360bbb-0) the following:

21 USC 360bbb-0a.

"SEC. 561B. INVESTIGATIONAL DRUGS FOR USE BY ELIGIBLE PATIENTS.

"(a) DEFINITIONS.—For purposes of this section—

"(1) the term 'eligible patient' means a patient-"(A) who has been diagnosed with a life-threatening disease or condition (as defined in section 312.81 of title 21, Code of Federal Regulations (or any successor regula-

"(B) who has exhausted approved treatment options and is unable to participate in a clinical trial involving the eligible investigational drug, as certified by a physician, who-

"(i) is in good standing with the physician's licensing organization or board; and "(ii) will not be compensated directly by the manu-

facturer for so certifying; and

"(C) who has provided to the treating physician written informed consent regarding the eligible investigational drug, or, as applicable, on whose behalf a legally authorized representative of the patient has provided such consent; "(2) the term 'eligible investigational drug' means an investigational drug (as such term is used in section 561)—

"(A) for which a Phase 1 clinical trial has been com-

"(B) that has not been approved or licensed for any use under section 505 of this Act or section 351 of the Public Health Service Act;

"(A) for which a Phase 1 clinical trial has been completed;

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"(C)(i) for which an application has been filed under section 505(b) of this Act or section 351(a) of the Public Health Service Act; or

"(ii) that is under investigation in a clinical trial that— "(I) is intended to form the primary basis of a claim of effectiveness in support of approval or licensure under section 505 of this Act or section 351 of the Public Health Service Act; and

"(II) is the subject of an active investigational new drug application under section 505(i) of this Act or section 351(a)(3) of the Public Health Service Act, as

applicable; and

"(D) the active development or production of which is ongoing and has not been discontinued by the manufacturer or placed on clinical hold under section 505(i); and "(3) the term 'phase 1 trial' means a phase 1 clinical investigation of a drug as described in section 312.21 of title 21, Code of Federal Regulations (or any successor regulations).

Definition of a 'phase 1 trial'

"(b) EXEMPTIONS.—Eligible investigational drugs provided to eligible patients in compliance with this section are exempt from sections 502(f), 503(b)(4), 505(a), and 505(i) of this Act, section 351(a) of the Public Health Service Act, and parts 50, 56, and 312 of title 21, Code of Federal Regulations (or any successor regulations), provided that the sponsor of such eligible investigational drug or any person who manufactures, distributes, prescribes, dispenses, introduces or delivers for introduction into interstate commerce, or provides to an eligible patient an eligible investigational drug pursuant to this section is in compliance with the applicable requirements set forth in sections 312.6, 312.7, and 312.8(d)(1) of title 21, Code of Federal Regulations (or any successor regulations) that apply to investigational drugs.

"(c) Use of Clinical Outcomes.—

"(1) IN GENERAL.—Notwithstanding any other provision of this Act, the Public Health Service Act, or any other provision of Federal law, the Secretary may not use a clinical outcome associated with the use of an eligible investigational drug pursuant to this section to delay or adversely affect the review or approval of such drug under section 505 of this Act or section 351 of the Public Health Service Act unless—

"(A) the Secretary makes a determination, in accordance with paragraph (2), that use of such clinical outcome is critical to determining the safety of the eligible investigational drug; or

"(B) the sponsor requests use of such outcomes.

"(2) LIMITATION.—If the Secretary makes a determination under paragraph (1)(A), the Secretary shall provide written notice of such determination to the sponsor, including a public health justification for such determination, and such notice shall be made part of the administrative record. Such determination shall not be delegated below the director of the agency center that is charged with the premarket review of the eligible investigational drug.

"(d) Reporting.—

"(1) IN GENERAL.—The manufacturer or sponsor of an eligible investigational drug shall submit to the Secretary an annual summary of any use of such drug under this section. The summary shall include the number of doses supplied, the Determination.

Notice. Records.

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Regulations.

21 USC 360bbb-0a note. number of patients treated, the uses for which the drug was made available, and any known serious adverse events. The Secretary shall specify by regulation the deadline of submission of such annual summary and may amend section 312.33 of title 21, Code of Federal Regulations (or any successor regulations) to require the submission of such annual summary in conjunction with the annual report for an applicable investigational new drug application for such drug.

"(2) POSTING OF INFORMATION.—The Secretary shall post an annual summary report of the use of this section on the internet website of the Food and Drug Administration, including the number of drugs for which clinical outcomes associated with the use of an eligible investigational drug

pursuant to this section was—

"(A) used in accordance with subsection (c)(1)(A);

"(B) used in accordance with subsection (c)(1)(B); and "(C) not used in the review of an application under section 505 of this Act or section 351 of the Public Health Service Act.".

(b) No Liability.—

- (1) ALLEGED ACTS OR OMISSIONS.—With respect to any alleged act or omission with respect to an eligible investigational drug provided to an eligible patient pursuant to section 561B of the Federal Food, Drug, and Cosmetic Act and in compliance with such section, no liability in a cause of action shall lie against—
 - (A) a sponsor or manufacturer; or
 - (B) a prescriber, dispenser, or other individual entity (other than a sponsor or manufacturer), unless the relevant conduct constitutes reckless or willful misconduct, gross negligence, or an intentional tort under any applicable State law.
- (2) DETERMINATION NOT TO PROVIDE DRUG.—No liability shall lie against a sponsor manufacturer, prescriber, dispenser or other individual entity for its determination not to provide access to an eligible investigational drug under section 561B of the Federal Food, Drug, and Cosmetic Act.
- (3) LIMITATION.—Except as set forth in paragraphs (1) and (2), nothing in this section shall be construed to modify or otherwise affect the right of any person to bring a private action under any State or Federal product liability, tort, consumer protection, or warranty law.

21 USC 360bbb-0a note.

SEC. 3. SENSE OF THE SENATE.

It is the sense of the Senate that section 561B of the Federal Food, Drug, and Cosmetic Act, as added by section 2—

 does not establish a new entitlement or modify an existing entitlement, or otherwise establish a positive right to any party or individual;

(2) does not establish any new mandates, directives, or additional regulations;

(3) only expands the scope of individual liberty and agency among patients, in limited circumstances;

(4) is consistent with, and will act as an alternative pathway alongside, existing expanded access policies of the Food and Drug Administration; $\underset{\text{tates}}{64}$

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132 STAT, 1375

(5) will not, and cannot, create a cure or effective therapy where none exists;

(6) recognizes that the eligible terminally ill patient population often consists of those patients with the highest risk of mortality, and use of experimental treatments under the criteria and procedure described in such section 561A involves an informed assumption of risk; and

(7) establishes national standards and rules by which investigational drugs may be provided to terminally ill patients.

Approved May 30, 2018.

Α

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The Dog Lab

Chapter

With many exotic new methods of conducting medical experiments including genetic testing and high technology in general, there remains a tried and true method of conducting the testing of innovative and potentially life-saving operations and procedures: the "dog lab." For the research physician, physiologist, and surgeon alike, the laboratory specializing in the use of large animals, e.g.: dogs, is the place that physicians are able to test procedures before they are attempted on human beings. Organ transplantation, the development of procedures using endoscopic instruments, the use of lasers to perform surgery on the human eye and even surgery through the use of remote controlled robots all had their beginnings in *The Dog Lab*.

Human nature is not only averse to being exposed to the grittiness of life but it collectively wretches in response to such exposures. As demonstrated by Hurricane Katrina in August of 2005, life's realities are stark, stomach turning and piercing. And yet, much of modern life is littered with a grittiness that we cannot indulge in the focus of the mind's eye. Whether it is the irresolvable nature and sordidness of abortion, the unimaginable, brutal and inhumane nature of the Nazi experiments on human beings or research of the Tuskegee Study of African Americans with syphilis in which penicillin was deliberately withheld in an effort to better understand how the disease is spread and what its effects are on the human body, we have little stomach for such mind numbing sordidness. The slaughtering of animals for their fur and for the protein flesh they provide for our daily fare comes even closer to scarring placid images of the good life as it is lived on a daily basis.

The use of dogs as vehicles for surgeons to learn how to perform new operations strikes a similar chord. It is abrasive to human consciousness to think that dogs are expendable for such purposes, especially since so many fellow citizens treasure them as family members. Dog labs are decades old and by nature experimental. Given their unsung role in the development of American surgical procedures, it is no small wonder that legions of dogs have

The Dog Lab

been sacrificed on the altar of learning. As such, dog labs have come to represent a slaughter house of sorts, a place where the life of an animal is put at risk or sacrificed for the good of learning how to do something that would be of benefit to human kind. Due to the bloody and unsavory light in which the dog lab has come to be cast in the minds of surgical medicine, the dog lab has come to represent disparaging metaphor of sometime unconscionable practices.

Many years ago, the term "dog lab" was used as an instructional metaphor to then this newly named Veterans Administration (VA) hospital's Chief of Surgery. A fellow senior surgeon offered the term as a description and an explanation of how some physicians have historically viewed the relationship between VA hospitals in general and the medical schools with which they affiliated over the course of the last sixty years. Thus, historically, the metaphor epitomizes the derogatory sentiments and allusions that some physicians and medical educators have made in the presence of their educational charges regarding the indigent and less-fortunate who are treated in our nation's largest public hospital system.

The callous use of such a demeaning metaphor signals nothing less than a diminishment of human worth. In the verbal attitudes they express, all too often medical educators as role models convey implied values that impart heavy and unfortunately lasting meaning for their students. It is the method by which values both ill and good are transmitted over the course of generations. Even if untrue1 initially and intended in reference to only one VA hospital, "The Dog Lab" is unimaginably derogatory to the U.S. Department of Veterans Affairs as an institution implying a substandard system of health care. Furthermore, it demeans and condemns those veterans who utilize the VA as their primary source of healthcare as somewhat less-than-human experimental subjects. And yet, it is the country's veterans who exposed themselves in harms' way to protect our way of life throughout our nation's history. It is those same veterans who knowingly served their country not knowing when they were inducted and swore allegiance to the country whether they would be stateside for the duration of their military career or die in combat within six months of their induction. It is those very same veterans to whom Abraham Lincoln 140 years ago promised on our behalf: "...to care for him who shall have borne the battle, and for his widow, and his orphan..." It is those veterans--the short, the long and the tall, the drug addicted or alcoholic, homeless, chronically mentally ill and rife with unrelenting PTSD--to whom we owe our way of life. The manner in which they are treated in the healthcare system dedicated to them reflects on the very character of our country.

¹VA hospitals have been recognized in recent studies as providing an above average standard of healthcare quality. See *U.S. News & World Report*. July 18, 2005

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	Chapter 3
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How to Lie With Statistics is a 65-year-old book that can be read in an hour and will teach you more practical information you can use every day than any book on "big data" or "deep learning." For all promised by machine learning and petabyte-scale data, the most effective techniques in data science are still small tables, graphs, or even a single number that summarize a situation and help us — or our bosses — make a decision informed by data.

Time and again, I've seen thousands of work hours on complex algorithms summarized in a single number. Ultimately, that's how the biggest decisions are made: with a few pieces of data a human can process. This is why lessons from "How to Lie with Statistics" (by Darell Huff) are relevant even though each of us probably generates more data in a single day than existed in the entire world at the writing of the book. As producers of tables and graphs, we need to effectively present valid summaries. As consumers of information, we need to spot misleading/exaggerated statistics which manipulate us to take action that benefits someone else at our expense.

These skills fall under a category called "data literacy": the ability to read, understand, argue with, and make decisions from information. Compared to algorithms or big data processing, data literacy may not seem exciting, but it should form the basis for any data science education. Fortunately, these core ideas don't change much over time and often the best books on the subject (such as The Visual Display of Quantitative Information) are decades old. The classic book discussed in this article addresses responsible consumption of data in a concise, effective, and enjoyable format. Here are my lessons learned from "How to Lie with Statistics" with commentary from my experiences.

4. Small Samples Produce Shocking Statistics

Would you be surprised if I told you the highest cancer rates tend to occur in the counties with the smallest populations? Not that shocking. How about when I add that the lowest cancer rates also tend to occur in counties with the lowest number of people? This a verified example of what occurs with small sample sizes: extreme values.

Any time researchers conduct a study, they use what is called a sample: a subset of the population meant to represent the entire population. This might work fine when the sample is large enough and has the same distribution of the larger population, but often, because of limited funding or response rates, psychological, behavioral, and medical studies are conducted with small samples, leading to results that are questionable and cannot be reproduced.

Scientists are usually limited to small samples by legitimate problems, but advertisers use small numbers of participants in their favor by conducting many tiny studies, one of which will produce a positive result. Humans are not great at adjusting for sample sizes when evaluating a study which in practice means we treat the results of a 1000 person trial the same as a 10 person trial. This is known as "insensitivity to sample size" or "sample size neglect".

8. Look for Bias in Sample Selection

Remember when we talked about all data being gathered from samples which we hope are representative of the population? In addition to being concerned about sample size, we also need to look for any bias in the sample.

This could come from the measurement method used: a landline phone screen might favor wealthier, older participants. It could also come from the physical location; surveying only people who live in cities because it's cheaper might bias results toward more progressive views. Sample bias is particularly prevalent in political polling where 2016 showed that sometimes samples are not representative of an entire population.

When examining a study, we need to ask who is being included in the sample and who is being excluded. For decades, psychology and sociology studies have been hurt by the WEIRD bias. Samples only included

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people (often college students) from Western, Education, Industrialized, Rich, Democratic, Nations. It's hard to reasonably say a survey represents all of humanity when the participants are this limited!

We should also look for sampling bias in our sources of information. Most of us now impose information selection bias on our selves by choosing sources that we tend to agree with. This leads to dangerous situations where we don't encounter people who have different opinions and so we grow more entrenched in our views. The solution to this is simple but difficult: read different sources of news, particularly those that don't agree with you.

If you are a New York Times reader, try the Wall Street Journal for a while. For those who are feeling adventurous, you can even try talking to people who disagree with you. While this may seem intimidating, I've found that people who disagree outwardly often have more in common — the same core driving desires — motivating them to choose their respective sides. It's much easier to come to a common understanding in person but even engaging in civil discourse online is possible and productive and can help you escape a self-imposed information-selection bias.

In summary, we need to be wary both of outside sampling bias and self-created sampling bias from our choice of media sources. You would not like someone telling you to read only a single newspaper, so don't do the same to yourself. Diverse viewpoints lead to better outcomes, and incorporating different sources of information with varying opinions will give you a better overall picture of events. We can't always get to the complete truth of a matter, but we can at least see it from multiple sides. Similarly, when reading a study, make sure you recognize that the sample may not be indicative of the entire population and try to figure out which way the bias goes.

9. Be Wary of "Big Names" on Studies and Scrutinize Authority

Huff describes the idea of an "O.K name" as one added to a study to lend it an air of authority. Medical professionals (doctors), universities, scientific institutions, and large companies have names that lead us to automatically trust the results they produce. However, many times these "experts" did not actually produce the work but only were tangentially involved and the name has been added to sway us. Other times, such as when cigarette makers used doctors to sell their deadly products, the <u>authorities are directly paid to lie</u>. One way to avoid being persuaded by an impressive name is to "make sure the name on the study stands behind the study and not beside it." Don't see an institutional name and immediately assume the study is infallible. I don't think we should look at the author or university until we've analyzed the statistics to avoid any unconscious bias we impose on ourselves.

Even when the results come from a confirmed "expert" that does not mean you should accept them without question. The <u>argument from authority</u> is a fallacy that occurs when we assume someone with greater power is more likely to be correct. This is false because past success has no bearing on whether current results are correct. As Carl Sagan put it: "Authorities must prove their contentions like everybody else." (<u>from The Demon-Haunted World</u>: Science as a Candle in the Dark).

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 - Serologic response to SARS-CoV-2
 - One study found the serologic response to a recombinant SARS-CoV-2 nucleocapsid: IgM 85.4%, IgA 92.7% (median 5d after the onset of symptoms), and IgG 77.9% (14d after onset).[22]
 - Another study from China using IgM and IgG SARS-CoV-2-specific antibodies found < 40% seropositive if illness less than 7d, rising to ~100% 15d or more after onset.</p>
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Abstract

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Cancer patients who have exhausted standard treatments often seek access to investigational drugs. Often, however, such access is unavailable, due to either the unavailability of a trial, lack of an open recruiting spot on the trial, even when the trial itself is open, or the inability of the patient to meet one or more trial eligibility criteria. In such settings patients often seek access to investigational agents outside of a trial. The federal "Right to Try" legislation was passed to create an additional avenue, different from the FDA's Expanded Access, or "Compassionate Use" Program, through which patients might obtain access to investigational drugs. A year after this legislation was signed into law, there remains both a limited awareness of it and a substantial degree of misunderstanding on the part of those who are aware of it. The law creates an avenue to greatly facilitate off-study administration when patient, physician and the manufacturer are all in agreement regarding the off study use of an eligible investigational agent. The law does not, however, empower a patient to impose a demand on either a provider or a drug manufacturer, nor does it require any entity to provide financial coverage for the drug. Eligible drugs are those which are not approved by the FDA for any indication, have completed a phase I trial, have an ongoing pivotal trial, and have an active registration plan. We review the specific law with commentary on its implications for improved access to investigational drugs outside of clinical trials.

Summary.

RTT creates a pathway for patients to receive an investigational drug outside of a clinical trial if, and only if, the patient is eligible, the drug is eligible, and the patient, drug manufacturer, and treating physician all agree that they wish to pursue this path. This legislation does not empower the patient to compel either a physician or a drug company to provide a drug under this Act. For the patient to be eligible, that patient must have a life- threatening disease or condition, must have exhausted standard care options, and must not have access to the drug on a clinical trial. For the drug to be eligible, it must not be approved by the FDA for any indication, must have completed a phase I trial, and must have an ongoing pivotal trial. The number of times in which all eligibility criteria for the patient and the drug are met, and all parties agree to proceed, will be limited, however, in such scenarios, RTT provides a pathway which is far simpler and requires far less consultation, documentation, and reporting than the FDA's Expanded Access Program, thus facilitating access to eligible investigational agents for eligible patients.

Table 1.

Summary of "Right to Try" Act

Requirements for Patient

- a. Life-threatening condition
- b. Exhausted standard treatment options
- c. Unable to participate in an ongoing trial
- d. Provide informed consent

Requirements for Drug

- a. Phase I trial completed
- b. Ongoing pivotal phase II or III trial
- c. Active development plan to seek FDA approval
- d. Not approved for any indication

Requirement for the Physician

- a. Be in good standing with licensing organization or board
- b. Certify that patient is unable to participate in a clinical trial involving the drug in question
- c. Accept written informed consent from patient or authorized representative.
- d. Receive no compensation from the Sponsor/manufacturer

Requirements for Sponsor/Manufacturer

a. Comply with standard procedures for investigational drug labeling, promotion,

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and recovery of direct costs.

b. Submit an annual summary of the use of the drug to the FDA, including number of doses supplied, number of patients treated, the uses for which the drug was made available, and any known serious adverse events.

Liabilities and Mandates

- a. No liability for a manufacturer's decision not to provide drug
- b. No liability for a physician's decision not to prescribe drug
- c. No mandate for any entity to provide coverage for drug or associated care
- d. No positive right established to any individual
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- 315) 2020-02-04 Hinton DM: From Revise EUA 091 of July 30, 2021. https://www.regeneron.com/downloads/treatment-covid19-eua-fda-letter.pdf https://www.fda.gov/media/145610/download

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19). ¹ On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.²

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https://www.reuters.com/article/us-china-health-hospital/chinese-doctors-using-plasma-therapy-on-coronavirus-who-says-very-valid-approach-idUSKBN20B1M6

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327) 2020-02-25 Paules CI, Marston HD, Fauci AS: Coronavirus Infections – More than just the Common Cold. JAMA. 2020 February 25; 323(8): 707-708.

https://pubmed.ncbi.nlm.nih.gov/31971553/

https://web.archive.org/web/20200606112925/https://jamanetwork.com/journals/jama/fullarticle/2759815

Human coronaviruses (HCoVs) have long been considered inconsequential pathogens, causing the "common cold" in otherwise healthy people. However, in the 21st century, 2 highly pathogenic HCoVs—severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)—emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality. In December 2019, yet another pathogenic HCoV, 2019 novel coronavirus (2019-nCoV), was recognized in Wuhan, China, and has caused serious illness and death. The ultimate scope and effect of this outbreak is unclear at present as the situation is rapidly evolving.

Coronaviruses are large, enveloped, positive-strand RNA viruses that can be divided into 4 genera: alpha, beta, delta, and gamma, of which alpha and beta CoVs are known to infect humans. Four HCoVs (HCoV 229E, NL63, OC43, and HKU1) are endemic globally and account for 10% to 30% of upper respiratory tract infections in adults. Coronaviruses are ecologically diverse with the greatest variety seen in bats, suggesting that they are the reservoirs for many of these viruses. Peridomestic mammals may serve as intermediate hosts, facilitating recombination and mutation events with expansion of genetic diversity. The surface spike (S) glycoprotein is critical for binding of host cell receptors and is believed to represent a key determinant of host range restriction. 1

Until recently, HCoVs received relatively little attention due to their mild phenotypes in humans. This changed in 2002, when cases of severe atypical pneumonia were described in Guangdong Province, China, causing worldwide concern as disease spread via international travel to more than 2 dozen countries. 2 The new disease became known as severe acute respiratory syndrome (SARS), and a beta-HCoV, named SARS-CoV, was identified as the causative agent. Because early cases shared a history of human-animal contact at live game markets, zoonotic transmission of the virus was strongly suspected. 3 Palm civets and raccoon dogs were initially thought to be the animal reservoir(s); however, as more viral sequence data became available, consensus emerged that bats were the natural hosts.

Common symptoms of SARS included fever, cough, dyspnea, and occasionally watery diarrhea.² Of infected patients, 20% to 30% required mechanical ventilation and 10% died, with higher fatality rates in older patients and those with medical comorbidities. Human-to-human transmission was documented,

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mostly in health care settings. This nosocomial spread may be explained by basic virology: the predominant human receptor for the SARS S glycoprotein, human angiotensin-converting enzyme 2 (ACE2), is found primarily in the lower respiratory tract, rather than in the upper airway. Receptor distribution may account for both the dearth of upper respiratory tract symptoms and the finding that peak viral shedding occurred late (≈10 days) in illness when individuals were already hospitalized. SARS care often necessitated aerosol-generating procedures such as intubation, which also may have contributed to the prominent nosocomial spread.

Several important transmission events did occur in the community, such as the well-characterized minioutbreak in the Hotel Metropole in Hong Kong from where infected patrons traveled and spread SARS internationally. Another outbreak occurred at the Amoy Gardens housing complex where more than 300 residents were infected, providing evidence that airborne transmission of SARS-CoV can sometimes occur.4 Nearly 20 years later, the factors associated with transmission of SARS-CoV, ranging from selflimited animal-to-human transmission to human superspreader events, remain poorly understood.

Ultimately, classic public health measures brought the SARS pandemic to an end, but not before 8098 individuals were infected and 774 died.2 The pandemic cost the global economy an estimated \$30 billion to \$100 billion. 1 SARS-CoV demonstrated that animal CoVs could jump the species barrier, thereby expanding perception of pandemic threats.

In 2012, another highly pathogenic beta-CoV made the species jump when Middle East respiratory syndrome (MERS) was recognized and MERS-CoV was identified in the sputum of a Saudi man who died from respiratory failure.³ Unlike SARS-CoV, which rapidly spread across the globe and was contained and eliminated in relatively short order, MERS has smoldered, characterized by sporadic zoonotic transmission and limited chains of human spread. MERS-CoV has not yet sustained community spread; instead, it has caused explosive nosocomial transmission events, in some cases linked to a single superspreader, which are devastating for health care systems. According to the World Health Organization (WHO), as of November 2019, MERS-CoV has caused a total of 2494 cases and 858 deaths, the majority in Saudi Arabia. The natural reservoir of MERS-CoV is presumed to be bats, yet human transmission events have primarily been attributed to an intermediate host, the dromedary camel.

MERS shares many clinical features with SARS such as severe atypical pneumonia, yet key differences are evident. Patients with MERS have prominent gastrointestinal symptoms and often acute kidney failure, likely explained by the binding of the MERS-CoV S glycoprotein to dipeptidyl peptidase 4 (DPP4), which is present in the lower airway as well as the gastrointestinal tract and kidney. 3 MERS necessitates mechanical ventilation in 50% to 89% of patients and has a case fatality rate of 36%.2

While MERS has not caused the international panic seen with SARS, the emergence of this second, highly pathogenic zoonotic HCoV illustrates the threat posed by this viral family. In 2017, the WHO placed SARS-CoV and MERS-CoV on its Priority Pathogen list, hoping to galvanize research and the development of countermeasures against CoVs.

The action of the WHO proved prescient. On December 31, 2019, Chinese authorities reported a cluster of pneumonia cases in Wuhan, China, most of which included patients who reported exposure to a large seafood market selling many species of live animals. Emergence of another pathogenic zoonotic HCoV was suspected, and by January 10, 2020, researchers from the Shanghai Public Health Clinical Center & School of Public Health and their collaborators released a full genomic sequence of 2019-nCoV to public databases, exemplifying prompt data sharing in outbreak response. Preliminary analyses indicate that 2019nCoV has some amino acid homology to SARS-CoV and may be able to use ACE2 as a receptor. This has important implications for predicting pandemic potential moving forward. The situation with 2019-nCoV is

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evolving rapidly, with the case count currently growing into the hundreds. Human-to-human transmission of 2019-nCoV occurs, as evidenced by the infection of 15 health care practitioners in a Wuhan hospital. The extent, if any, to which such transmission might lead to a sustained epidemic remains an open and critical question. So far, it appears that the fatality rate of 2019-nCoV is lower than that of SARS-CoV and MERS-CoV; however, the ultimate scope and effects of the outbreak remain to be seen.

Drawing on experience from prior zoonotic CoV outbreaks, public health authorities have initiated preparedness and response activities. Wuhan leaders closed and disinfected the first identified market. The United States and several other countries have initiated entry screening of passengers from Wuhan at major ports of entry. Health practitioners in other Chinese cities, Thailand, Japan, and South Korea promptly identified travel-related cases, isolating individuals for further care. The first travel-related case in the United States occurred on January 21 in a young Chinese man who had visited Wuhan.

Additionally, biomedical researchers are initiating countermeasure development for 2019-nCoV using SARS-CoV and MERS-CoV as prototypes. For example, platform diagnostic modalities are being rapidly adapted to include 2019-nCoV, allowing early recognition and isolation of cases. Broad-spectrum antivirals, such as remdesivir, an RNA polymerase inhibitor, as well as lopinavir/ritonavir and interferon beta have shown promise against MERS-CoV in animal models and are being assessed for activity against 2019-nCoV.5 Vaccines, which have adapted approaches used for SARS-CoV or MERS-CoV, are also being pursued. For example, scientists at the National Institute of Allergy and Infectious Diseases Vaccine Research Center have used nucleic acid vaccine platform approaches. 6 During SARS, researchers moved from obtaining the genomic sequence of SARS-CoV to a phase 1 clinical trial of a DNA vaccine in 20 months and have since compressed that timeline to 3.25 months for other viral diseases. For 2019-nCoV, they hope to move even faster, using messenger RNA (mRNA) vaccine technology. Other researchers are similarly poised to construct viral vectors and subunit vaccines.

While the trajectory of this outbreak is impossible to predict, effective response requires prompt action from the standpoint of classic public health strategies to the timely development and implementation of effective countermeasures. The emergence of yet another outbreak of human disease caused by a pathogen from a viral family formerly thought to be relatively benign underscores the perpetual challenge of emerging infectious diseases and the importance of sustained preparedness.

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Article Information

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Conflict of Interest Disclosures: None reported.

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 https://trumpwhitehouse.archives.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/

DR. SCHLEIFER: Thanks, Mr. President, for having us. I'm Lenny Schleifer, the founder and CEO of Regeneron, a company that I built with George Yancopoulos over the last 30 years. And we are a monoclonal antibody primarily centered company. We are no strangers to collaborating with the administration. We work with Secretary Azar's group, BARDA. And we came up with a cure for Ebola, and we're very proud of that. Dr. Fauci's group was really instrumental in testing that under unbelievable conditions in the Congo. And it didn't create quite as much excitement, because, thank goodness, it didn't hit our shores.

But we can use the exact same technology, and we already have. We have 1,000 antibodies that are already sitting in dishes. We're screening them. We're selecting them. We anticipate, if all goes well, 200,000 doses per month can come out of our factory in New York, starting in August.

The unique thing about our technology —

THE PRESIDENT: That means you'd be able to use the vaccine that early?

DR. SCHLEIFER: It depends on what we see; how we work closely with the FDA, which we will do. The FDA already reached out to us, but we've got to work closely.

THE PRESIDENT: So that process would be faster than John's?

DR. SCHLEIFER: It would be. The —

SECRETARY AZAR: Can you explain why that would be?

DR. SCHLEIFER: Well, so, we make passive vac—vaccine and therapeutic—therapeutic. Our drug will be able to protect you. Whether or not you're infected, it'll protect you from getting infected. Or if you are infected, it would treat you. And the — we have just taken processes that normally take years—literally, years — and we put them end-to-end and now do them in weeks to months, which nobody else in the industry can do.

So we're very excited to collaborate once again.

THE PRESIDENT: So this would be a combination of a vaccine and also it will — to put it in a different way — make you better, quicker.

DR. SCHLEIFER: Yeah. Well, think of it this way: If you — if you get immunized with one of these vaccines, you're going to make some antibodies to protect you. We're going to already make those antibodies and give them to you so you don't have to go through that whole process. So it'll protect you.

And, as we showed with Ebola, if you give enough of them — we — it was lifesaving, life- — truly lifesaving.

THE PRESIDENT: That's true.

DR. SCHLEIFER: And it beat out the antivirals. It really — it was the way to go. It's very predictable.

I just want to say, I hope everybody succeeds here. I mean, this is — bringing everybody together here is really critical and there's going to be success. This industry is really talented, as an industry. Sometimes we run astray, but we're going to get this done.

THE PRESIDENT: Thank you very much. Thanks, Len. Appreciate it. Please.

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Dr. Leonard Schleifer, Regeneron Pharmaceuticals CEO, explains that, no, vaccines are vaccines and drugs are drugs. Dr. Schleifer: Well, think of it this way, if you get immunized with one of these vaccines, you're going to make antibodies to protect you. We are going to give you those antibodies so you don't have to go through that process.

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2020-03-02 Facher L: Trump's tone toward pharma shifts, as he looks to drug makers to help with coronavirus response. StatNews. https://www.statnews.com/2020/03/02/trumpstone-toward-pharma-shifts-coronavirus/

> WASHINGTON — President Trump had billed the meeting with pharmaceutical executives as a scolding waiting to happen. The gathering was intended to pressure the industry to bring drug prices "way down," he said on Friday, suggesting it had only later morphed into a "convenient" opportunity to discuss the development of a coronavirus vaccine.

But seated across from 10 pharmaceutical executives in the Cabinet Room on Monday, Trump's long-simmering contempt for the drug industry melted away. Trump told executives from Gilead, Johnson & Johnson, and Pfizer that they worked for a "great company." He affectionately referred to Leonard Schleifer, the CEO of Regeneron, as "Lenny." At one point, Trump referred to the assembled drug executives as "geniuses."

The meeting signified a remarkable shift in Trump's view of the pharmaceutical industry. After years of maintaining that drug companies charge "ripoff" prices, Trump appeared floored by the executives' progress reports. He alternatingly praised CEOs and egged them on to lay out shorter and shorter timelines for bringing a vaccine to market. Trump, throughout the meeting, appeared so blown away by the drug companies' claims that his deputies struggled to rein in his expectations.

"Like I've been telling you, Mr. President," Tony Fauci, the director of the National Institute on Allergy and Infectious Disease, interjected at one point. "A year to a year and a half," he said, referring to the amount of time it will likely take to deploy an effective vaccine to large populations.

Undeterred, Trump continued to ask various versions of the same question: "So what do you think in terms of timing?"

The executives largely told the president what he wanted to hear — that for both therapies and vaccines, companies could enter early testing within months, with the aim of reaching the market in time for peak season in a year's time.

"It was: Tell us how fast you can go, but let's keep safety in mind, and let's make sure we create something manufacturable," said Dan Menichella, CEO of CureVac, who was among the executives seated before Trump. The company, headquartered in Germany and Boston, uses messenger RNA to produce protective antibodies inside patients' bodies, thereby preventing infection. CureVac expects to start testing its coronavirus vaccine in healthy volunteers by June, with further trials to come if the injection proves safe.

But even as Fauci and health secretary Alex Azar interrupted to caution the president that most therapies and vaccines were nowhere near ready, the president leaned into the executives' positive spin.

"That's very exciting," Trump said at one point to Daniel O'Day, the CEO of the biotech giant Gilead Sciences, after he described progress on a therapy that could be used to mitigate coronavirus symptoms. "Get it done, Daniel. Don't disappoint us."

Fueling Trump's optimism: When questioned by the president, drug company representatives often struggled to differentiate between projections for bringing drugs to late-stage trials and bringing them to market — so much so that Fauci became a de facto referee.

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At one point, he responded to Stephane Bancel, the chief executive officer of Moderna, with a stern clarification: "You won't have a vaccine — you'll have a vaccine to go into testing."

But he immediately pivoted to Regeneron's Schleifer.

"But Lenny is talking about two months," Trump replied. "I mean, I like the sound of a couple of months better."

- 335) 2020-03-03 pharmaphorum: CEOs give Trump 'Biology 101' lesson as coronavirus causes election nerves. https://pharmaphorum.com/news/ceos-give-trump-biology-101-lesson-as-coronavirus-causes-election-nerves/
 - The meeting turned into a kind of Biology 101 lesson for a perplexed-looking Trump from the likes of <u>GlaxoSmithKline</u>'s CEO Emma Walmsley, Gilead's CEO Daniel O'Day, Johnson & Johnson's chief scientific officer Paul Stoffels, and Regeneron's CEO Leonard Schleifer.
 - ii. Health secretary Alex Azar kicked off the meeting by asking the pharma execs to find ways to hasten development of a vaccine.
 - iii. And there was a sense of tension in the room as it became apparent that it's unlikely one will be approved and ready to use ahead of the presidential elections in November.
 - iv. In a progress briefing from Schleifer, Trump praised Regeneron for its progress so far before asking whether a flu vaccine would work against COVID-19.
 - v. Trump said: "You take a solid flu vaccine you don't think that would have an impact or much of an impact on corona?"
 - vi. The answer from Schleifer was a flat "no", with Anthony Fauci from the National Institutes for Healthcare softening the blow with "probably not".
 - vii. Trump asked <u>Gilead's O'Day</u> to hurry trials of its antiviral drug <u>remdesivir</u> begun this week, telling the CEO to "get it done".
 - viii. He added: "Don't disappoint us, Daniel. Do you understand? Great company. Really great."
 - ix. Trump also quizzed J&J's Stoffels about the timeline for the development of that company's vaccine and noted that the US pharma's vaccine will not be ready until next
 - x. Azar went on to lay out a time frame for development of various therapeutic options for the president, noting that antivirals will likely be ready first, ahead of monoclonal antibodies from Regeneron, followed by vaccines.
 - xi. Summarising, Trump said: "I will tell you, the whole thing with therapeutics, to me, is very exciting. And, obviously, vaccines. But therapeutics is very exciting, especially when you're so far advanced. That's great. That's really great. Thank you."
- 336) 2020-03-05. YouTube: Regeneron's Leonard S. Schleifer meets with Trump at the White House, 3/2/2020. https://www.youtube.com/watch?v=31i6p_stzW8 AT THIS MEETING, PRESIDENT TRUMP AND ALL THE PEOPLE OF THE WORLD WERE MISLED BY OMISSION / MISREPRESENTING THE DISTINCTION BETWEEN ACTIVE IMMUNIZATION (vaccines) versus PASSIVE IMMUNIZATION (convalescent plasma, convalescent sera, monoclonal antibodies, monoclonal antibody cocktail, etc.). The cost of production of a dose (1/2 unit of fresh frozen plasma) COVID-19 Convalescent Plasma (CCP) which was available in March 2020 is ~\$200 while a dose of

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REGEN-COV[™] (Casirivimab with imdevimab) which would be several months into the future and would cost ~\$3000 a dose. A monoclonal antibody is specific for one antigen (e.g. a specific site on the spike point) and is likely to be ineffective on future variants like Omicron. Polyclonal antibodies like Convalescent Plasma will have multiple antibodies of such sites as on the spike protein and will be available as the SARS-CoV-2 mutates. (e.g. more effective on the Omicron variant).

****** Full 56:54 minute meeting in *The White House* where they went around the table introducing the key players: https://www.c-span.org/video/?469926-1/president-trump-meeting-pharmaceutical-executives-coronavirus with the complete transcript: https://web.archive.org/web/20200303160403/https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/">https://web.archive.org/web/20200303160403/https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/">https://web.archive.org/web/20200303160403/https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/ This https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/ This https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/ This https://www.whitehouse.gov/briefings-statements/remarks-president-trump-members-coronavirus-task-force-meeting-pharmaceutical-companies/ This https://www.whitehouse.gov/

Individuals at the White House meeting of March 2, 2020.

President Donald Trump, 2 years Fordham University and the 2 years Wharton School of the University of Pennsylvania, B.S. in Economics

Alexander Azar, Secretary of the U.S. Department of Health and Human Services, summa cum laude in government and economics from Dartmouth and J.D. from Yale University

Emma Walmsley , CEO of GlaxoSmithKline, MA in Classics and Modern Languages from Oxford University (Christ Church)

Anthony Fauci, M.D., Director of the NIAID of the NIH, College of the Holy Cross with a BA in classics and a MD from Cornell University graduating 1st in his class

Robert Redfield, M.D., Director of the CDC, graduated from Georgetown University's College of Arts and Sciences with a BS and MD from Georgetown University School of Medicine

Daniel Menichella, CEO of CureVac, BA in economics from Harvard University and a MBA from University of North Carolina at Chapel Hill

John Shiver, PhD, Senior Vice President, Vaccines Global R&D at Sanofi Vaccines, BS in Chemistry/Mathematics, Woffard College and a PhD in Chemistry from the University of Florida

Leonard Schleifer, M.D., PhD, CEO Regeneron, BS at Cornell University and an MD-PhD from the University of Virginia

Stephane Bancel, CEO of Moderna, masters degrees from both CentraleSupélec of Paris-Saclay University (engineering) and the University of Minnesota (biological engineering) and an MBA from Harvard Business School

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Daniel O'Day, BS, MBA, Chairman and CEO of Gilead Sciences has a BS in biology from Georgetown University and an MBA from Columbia University in New York

Steven Hahn, M.D., Commissioner, U.S. Food and Drug Administration, BA in Biology from Rice University and MD from Temple University

Mikael Dolsten, M.D., Ph.D., Chief Scientific Officer of Pfizer, Ph.D. in tumor immunology and a MD from Lund University

Joseph Kim, Ph.D., Inovio Pharmaceuticals, BS degrees in Chemical Engineering and Economics from MIT, a Ph.D. in immunology from the University of Pennsylvania, and an MBA in finance from the Wharton School of Business, University of Pennsylvania

Paul Stoffels, M.D., Chief Scientific Officer of Johnson & Johnson, studied medicine at the University of Diepenbeek and the University of Antwerp in Belgium and Infectious Diseases and Tropical Medicine at the Institute of Tropical Medicine in Antwerp, Belgium.

Anne Schuchat, M.D., Principal Deputy Director of the CDC, Swarthmore College and MD Dartmouth Medical School

Stanley Erck, President and CEO of Novavax, undergraduate degree from the University of Illinois and MBA in economics and finance from the Booth School of Business, The University of Chicago

Ambassador Deborah Birx, M.D., U.S. Department of State, BS in chemistry from Houghton College and MD from Pennsylvania State University.

- 337) 2020-03-05 Herper M, Feuerstein A: How blood plasma from recovered patients could help treat the new coronavirus. STATnews Mar 5, 2020, 1-7.

 https://www.statnews.com/2020/03/05/how-blood-plasma-from-recovered-patients-could-help-treat-coronavirus/
- 338) 2020-03-09 Johns Hopkins University & Medicine Coronavirus Resource Center: First date documented by the Internet Archive (Wayback Machine: https://archive.org/web/) to have been published. https://coronavirus.jhu.edu/map.html
- 339) 2020-03-09 U.S. Department of Health & Human Services, Centers for Medicare and Medicaid Services: Center for clinical standards and quality/quality, safety and oversight group. Ref: QSO-20-15 Hospital/CAH/EMTALA https://www.cms.gov/files/document/qso-20-15-hospitalcahemtala.pdf
- 340) 2020-03-11 Downs Burger J: Novel coronavirus: EMTALA compliance for hospitals with dedicated emergency departments. Arnall, Golden, Gregory LLP https://www.agg.com/news-insights/publications/novel-coronavirus-emtala-compliance-for-hospitals-with-dedicated-emergency-departments-2/

On March 9, 2020, CMS issued a memorandum to State Survey Agency Directors regarding the implications of COVID-19 on providers' EMTALA obligations. In addition to confirming the

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recommendations in our March 6 Client Alert below, the CMS memorandum provides further guidance that hospitals with dedicated emergency departments should review. We highlight a few notable items below.

Hospital Signage: CMS emphasized that it is a violation of EMTALA for hospitals to use signage that presents barriers to individuals who are suspected of having COVID-19 from coming to the emergency room. However, use of signage designed to help direct individuals to various locations on the hospital property for their Medical Screening Exam – such as an alternative screening location – would be acceptable.

What if an individual who meets the screening criteria for suspected COVID-19 wants to leave the hospital against medical advice? Hospitals cannot prevent the individual from leaving against medical advice. However, State or local public health authorities may have such authority under State or local law. Hospitals should coordinate with their local authorities on the appropriate way to handle such situations.

How will CMS handle complaints about violations of EMTALA in connection with individuals presenting with symptoms of COVID-19? CMS states that it will consider the following (along with other factors) when making a determination of whether violations of EMTALA have occurred:

- The individual's clinical condition at the time of presentation to the referring hospital and at the time of the transfer request;
- The capabilities of the referring hospital;
- The screening and treatment activities performed by the referring hospital for the individual;
- Whether the request for transfer was consistent with any nationally recognized guidelines in effect at the time of the transfer request for COVID-19 screening, assessment, including guidance about transfer for further assessment or treatment of suspected or confirmed COVID-19; and
- The capabilities of the recipient hospital and the recipient hospital's capacity at the time of the transfer request.

What will CMS do if a hospital is not following nationally recognized guidelines regarding COVID-19 infection control processes? While EMTALA does not establish requirements for infection control practices, hospitals are expected to adhere to accepted standards of infection control practice and as part of the conditions of participation for Federal health care programs. CMS cautions that hospitals may be cited for deficiencies related to failure to follow accepted infection prevention and control standards of practice. As such, CMS strongly urges hospitals to follow CDC guidance related to COVID-19 infection control procedures. Hospitals should regularly check the official CDC website and consider signing up for the newsletter to receive weekly emails about COVID-19

Novel coronavirus ("2019-nCoV", also known as "SARS-CoV-2") and the disease it causes – "coronavirus disease 2019" (abbreviated as "COVID-19") has garnered significant public attention since being declared

a Public Health Emergency of International Concern by the World Health Organization, and a public health emergency in the United States by the Department of Health and Human Services ("HHS"). Of particular significance to healthcare providers' compliance efforts is whether the President's observation and monitoring of the situation will culminate in a declaration by the President of a national emergency in connection with the incidences of novel coronavirus.

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In the event of a declaration of a national emergency by the President, the requirements of the Emergency Medical Treatment and Labor Act ("EMTALA") may be formally suspended. However, in the absence of such a declaration by the President and a formal suspension of EMTALA, hospitals are required to comply with EMTALA provisions and may be sanctioned for non-compliance. The Centers for Medicare and Medicaid Services ("CMS") has made recommendations regarding the ways in which hospital emergency departments may take adequate precautions in circumstances like these, while also complying with EMTALA mandates in the absence of a formal suspension. We outline these frameworks in further detail below.

What is EMTALA?

EMTALA is a federal law that requires all Medicare-participating hospitals with a dedicated emergency department to take certain actions when any individual comes to the emergency department and requests an examination or treatment of a medical condition, or when such a request is made on the individual's behalf, regardless of the individual's ability to pay. EMTALA was enacted to prevent hospitals from "dumping" patients because the patients could not pay for treatment, or because of other discriminatory purposes. If a hospital is subject to EMTALA, then it must perform an appropriate medical screening exam ("MSE") on the individual to determine if an emergency medical condition ("EMC") exists. The content of the MSE may vary based on the individual's presenting signs and symptoms, so long as the MSE is sufficient to rule out that an EMC exists. The MSE must be performed by qualified personnel, including a physician, physician assistant, nurse practitioner, or registered nurse who is trained to perform MSEs and who is acting within their state's scope of practice. If an EMC does exist, then the hospital must treat and stabilize the EMC within its capabilities to do so, or alternatively, transfer the individual to a hospital that has the capability and capacity to stabilize the EMC. If an EMC does not exist, then the hospital's obligations with regard to EMTALA end.

When Are a Hospital's EMTALA Obligations Suspended During a National Emergency?

It seems to be a common misconception that when a state's governor has declared a state of emergency in response to a disease outbreak (whether COVID-19, the flu, or otherwise), a hospital's MSE and stabilization obligations under EMTALA have been suspended. However, in such situations, a well-meaning hospital can find itself in violation of EMTALA.

In order for a hospital's MSE and stabilization obligations to be suspended, the federal government must first take four formal actions under Section 1135 of the Social Security Act ("Section 1135"):

- 1. The President, and not the state's governor, must have declared an emergency or a disaster under either the Stafford Act or the National Emergencies Act;
- 2. The Secretary of Health and Human Services (the "Secretary") must have declared a public health emergency;
- 3. The Secretary must have invoked his or her waiver authority, which includes giving Congress 48 hours' advance notice; and
- 4. The Secretary must issue a waiver that would cover the hospital and includes a specific waiver of the EMTALA requirements.

Then, the hospital's state must have formally activated its emergency or pandemic preparedness plan and any redirection or transfer of individuals must be consistent with this plan. Additionally, the EMTALA waiver will not apply to a hospital that has not activated its own disaster protocol.

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When such a waiver is issued, CMS is to provide notice to covered hospitals through its Regional Offices or State Survey Agencies. When an EMTALA waiver is issued for a public health emergency caused by a pandemic infectious disease, such as novel coronavirus, the EMTALA waiver remains in place until the Secretary terminates the declaration of the public health emergency.

What Obligations under EMTALA May be Suspended by a Waiver?

As alluded to above, Section 1135 allows the Secretary to waive the sanctions associated with a hospital for redirecting an individual to an alternative location for the MSE pursuant to a state emergency or pandemic preparedness plan that would otherwise not be allowed under EMTALA. The Secretary may also waive sanctions for a hospital's inappropriate transfer if the transfer was necessitated by the circumstances of the declared emergency. This typically allows a hospital to avoid sanctions when it transfers a patient before the EMC is stabilized. However, a hospital may not discriminate among individuals based on their ability to pay or their payor source while under a waiver. Sanctions for all other EMTALA requirements may not be waived. It is also important to note that a Section 1135 waiver does not, in and of itself, relieve the hospital from any obligations under state or local laws. Note that if a waiver is issued, it only waives the sanctions applicable to the hospital under EMTALA. Therefore, if an individual is harmed by a hospital's negligent transfer or redirection performed under a waiver, then the hospital may be liable to the individual for that harm.

Can a Hospital Request a Waiver if One Has Not Been Issued?

Yes. If an EMTALA waiver has not yet been issued that covers a hospital, then the hospital may request a waiver under Section 1135. Before CMS will consider a waiver request, the federal government must have performed the first three formal actions outlined above. Furthermore, the Secretary must have delegated his or her decision-making regarding EMTALA to CMS. The hospital, or the hospital's representative, typically makes the waiver request to the CMS Regional Office for the region in which the hospital is located.

What are a Hospital's Options if a Waiver is Not Granted?

If a waiver is not granted, hospitals have a couple of options to separate patients presenting with symptoms of COVID-19 in the emergency department, while continuing to meet EMTALA mandates.

Option 1: Set Up On-Campus Alternative Screening Sites. A hospital is not required to perform the MSE within the emergency department itself. A hospital could instead set up alternative sites on its campus to perform certain MSEs. The patient would need to be logged into the emergency department before being redirected to the alternative site, but this process could take place outside of the entrance to the emergency department. CMS recommends that if a hospital implements such a process, then the persons redirecting patients to the alternative site should be qualified to recognize patients who are obviously in need of emergency treatment (for example, a registered nurse). The MSEs performed at the alternative site must meet all the requirements for MSEs required by law.

Option 2: Set Up Off-Campus Alternative Screening Sites. A hospital may set up a screening site that is not on its campus, as long as the location remains under the hospital's control. This arrangement makes compliance with EMTALA somewhat riskier than the first option. The hospital could not, for instance, redirect individuals who have already come to the emergency department to the off-campus location. The hospital could prospectively encourage the general public to go to the off-campus location for screenings related to COVID-19 and/or influenza, and could publically hold out that the location serves a screening center for that specific purpose. In doing so, however, the hospital could not hold the location out as a place that provides care or screening for EMCs in general on an urgent, unscheduled basis. As long as the off-

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campus site is not itself a dedicated emergency department, then EMTALA does not apply to the visit. Significantly, the site should still be staffed by medical personnel qualified to evaluate individuals presenting with symptoms of COVID-19 and/or flu-like symptoms.

Conclusion

Certain EMTALA obligations may be waived during a national emergency when the federal government takes formal actions specified in the Social Security Act. This waiver only applies to hospitals that (1) are located in states that have formally activated their emergency or pandemic preparedness plan and (2) have activated their own disaster protocol. Even under a waiver, hospitals must continue to meet all non-waived EMTALA obligations. If a waiver has not been issued, then a hospital may apply to CMS for a waiver. If a waiver is not granted, then the hospital may redirect individuals to an alternative screening site located on the hospital's campus so long as all EMTALA requirements are met. A hospital may also set up alternative screening sites off of its campus; however, patients who have already presented to the emergency department may not be redirected to these sites.

If you have any questions about whether your emergency department's operational plan or disaster protocol is compliant with EMTALA or would like assistance requesting a Section 1135 waiver, please contact Jennifer Burgar, Ryan Kerr or Nirouz Elhammali.

Summary and Practical Tips for EMTALA Compliance

- The federal government can waive certain EMTALA requirements during a declared public health emergency.
- Federal and state governments and the hospital must take specific formal actions before these requirements are waived.
- The Secretary of HHS may only waive the sanctions associated with redirecting individuals for their medical screening exam and for transfer that would otherwise be inappropriate under EMTALA.
- If an individual is redirected for a medical screening exam or is inappropriately transferred under a waiver, then the redirection or transfer must not have been made for a discriminatory purpose.
- A hospital must continue to meet all other EMTALA obligations.
- The hospital remains liable in legal actions by individuals who are harmed by redirection or transfers made under a waiver.
- A hospital can request a waiver from CMS if one has not been granted.
- Without a waiver, a hospital may redirect patients for a COVID-19 or other influenza-like illness screening to an alternative on-campus location so long as the hospital's EMTALA obligations continue to be met
- Without a waiver, a hospital may make off-campus locations available for such illness screenings
 so long as the location is under the control of the hospital and individuals who come to the
 emergency department are not redirected to these locations.

341)	2020-03-13 Casadevall A, Pirofski L:	The convalescent sera option for containing
CC	OVID-19. [jci.org, Journal of Clinical I	nvestigation 130 (4); April 2020: 1545-1548].
<u>htt</u>	ps://www.jci.org/articles/view/138003.	https://www.jci.org/articles/view/138003/pdf

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A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutrallizing the initial inoculum, which is likely to be much smaller than that of established disease (5). Another explanation is that antibody works by modifying the inflammatory response, which is also more easily achieved during the initial immune response, which is also more easily achieved during the initial immune response, a stage that may be asymptomatic (6). ...

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues, and provide protective against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months.....

Figure 1. Schematic of the use of convalescent sera for COVID-19. An individual who is sick with COVID-19 and recovers has blood drawn and screened for virus-neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, serum containing these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infections in high-risk cases, such as vulnerable individuals with underlying medical conditions, health care providers, and individuals with exposure to confirmed cases of COVID-19. Additionally, convalescent serum could potentially be used in individuals with clinical disease to reduce symptoms and mortality. The efficacy of these approaches is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than the treatment of established disease

342) 2020-03-13 Hixenbaugh M: Doctors push for treatment of coronavirus with blood from recovered patients. NBC News, March 12, 2020. https://www.nbcnews.com/health/health-care/doctors-push-treatment-coronavirus-blood-recovered-patients-n1158476

When Casadevall learned in December that a new coronavirus was spreading rapidly in China, he stared telling colleagues that it might be time to revive the antiquate treatment.

"I'm an infectious disease doctor who is interested in history," Casadevall said. "I knew the history of what was done in the early 20^{th} century with epidemics. The didn't have vacccines then, they didn't have any drugs then – just like the situation we face now. But physicians then knew that, for certain conditions, you could take the blood of the immune and use it to prevent disease or treat those who became ill."

In a paper published Friday in the Journal of Clinical Investigation, Casadevall and a colleague, Dr. Liise-anne Pirofski argued that collecting blood serum or plasma from previously infected people might be the best hope for treating severe cases of COVID-19, the disease caused by the virus, at least until a better treatment can be developed.

343) 2020-03-13 Trump DJ: Proclamation on declaring a national emergency concerning the novel coronavirus disease (COVID-19) outbreak. The White House. https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/

Section 1. Emergency Authority. The Secretary of HHS may exercise the authority under section 1135 of the SSA to temporarily waive or modify certain requirements of the Medicare, Medicaid, and State Children's Health Insurance programs and of the Health Insurance Portability and

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Accountability Act Privacy Rule throughout the duration of the public health emergency declared in response to the COVID-19 outbreak.

2020-03-13 Azar AM: Waiver or modification of requirements under section 1135 of the Social Security Act.

www.phe.gov/emergency/news/healthactions/section1135/Pages/covid19-13March20.aspx de facto, I allege that the interpretation of this document became the justification of abridgement of individual American rights to Passive Immunization and the antiviral drug Remdesivir, guaranteed under EMTALA (the Emergency Medical Treatment and Labor Act of COBRA, Consolidated Omnibus Budget Act of 1986, PL-99-272), and the Right to Tray Act of 2018, PL-115-176. Copied verbatim:

Waiver or Modification of Requirements Under Section 1135 of the Social Security Act

March 13, 2020

- Pursuant to Section 1135(b) of the Social Security Act (the Act) (42 U.S.C. § 1320b-5), I, Alex M. Azar II, Secretary of Health and Human Services, hereby waive or modify the following requirements of titles XVIII, XIX, and XXI of the Act and regulations thereunder, and the following requirements of Title XI of the Act, and regulations thereunder, insofar as they relate to Titles XVIII, XIX, and XXI of the Act, but in each case, only to the extent necessary, as determined by the Centers for Medicare & Medicaid Services, to ensure that sufficient health care items and services are available to meet the needs of individuals enrolled in the Medicare, Medicaid and CHIP programs and to ensure that health care providers that furnish such items and services in good faith, but are unable to comply with one or more of these requirements as a result of the consequences of the 2019 Novel Coronavirus (previously referred to as 2019nCoV, now as COVID-19) pandemic, may be reimbursed for such items and services and exempted from sanctions for such noncompliance, absent any determination of fraud or abuse:
 - Certain conditions of participation, certification requirements, program participation or similar requirements for individual health care providers or types of health care providers, including as applicable, a hospital or other provider of services, a physician or other health care practitioner or professional, a health care facility, or a supplier of health care items or services, and pre-approval requirements.
 - b. Requirements that physicians or other health care professionals hold licenses in the State in which they provide services, if they have an equivalent license from another State (and are not affirmatively barred from practice in that State or any State a part of which is included in the emergency area).
 - Sanctions under section 1867 of the Act (the Emergency Medical Treatment and Labor Act, or EMTALA) for the direction or relocation of an individual to another location to receive medical screening pursuant to an appropriate state emergency preparedness plan or for the transfer of an individual who has not been stabilized if the transfer is necessitated by the circumstances of the declared Federal public health emergency for the COVID-19 pandemic.
 - Sanctions under section 1877(g) (relating to limitations on physician referral) under such conditions and in such circumstances as the Centers for Medicare & Medicaid Services determines appropriate.
 - Limitations on payments under section 1851(i) of the Act for health care items and services furnished to individuals enrolled in a Medicare Advantage plan by health care professionals or facilities not included in the plan's network.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

----- May 30, 2022 -----

- 2. Pursuant to Section 1135(b)(7) of the Act, I hereby waive sanctions and penalties arising from noncompliance with the following provisions of the HIPAA privacy regulations: (a) the requirements to obtain a patient's agreement to speak with family members or friends or to honor a patient's request to opt out of the facility directory (as set forth in 45 C.F.R. § 164.510); (b) the requirement to distribute a notice of privacy practices (as set forth in 45 C.F.R. § 164.520); and (c) the patient's right to request privacy restrictions or confidential communications (as set forth in 45 C.F.R. § 164.522); but in each case, only with respect to hospitals in the designated geographic area that have hospital disaster protocols in operation during the time the waiver is in effect.
- 3. Pursuant to Section 1135(b)(5), I also hereby modify deadlines and timetables and for the performance of required activities, but only to the extent necessary, as determined by the Centers for Medicare & Medicaid Services, to ensure that sufficient health care items and services are available to meet the needs of individuals enrolled in the Medicare, Medicaid and CHIP programs and to ensure that health care providers that furnish such items and services in good faith, but are unable to comply with one or more of these requirements as a result of the COVID-19 pandemic, may be reimbursed for such items and services and exempted from sanctions for such noncompliance, absent any determination of fraud or abuse.

These waivers and modifications will become effective at 6:00 P.M. Eastern Standard Time on March 15, 2020, but will have retroactive effect to March 1, 2020, nationwide, and continue through the period described in Section 1135(e). Notwithstanding the foregoing, the waivers described in paragraph 2 above are in effect for a period of time not to exceed 72 hours from implementation of a hospital disaster protocol but not beyond the period described in Section 1135(e). The waivers described in paragraphs 1(c) and 2 above are not effective with respect to any action taken thereunder that discriminates among individuals on the basis of their source of payment or their ability to pay.

The waivers and modifications described herein apply in the geographic area covered by the President's proclamation, pursuant to the National Emergencies Act, on March 13, 2020, that the COVID-19 outbreak in the United States constitutes a national emergency; and my January 31, 2020, determination, pursuant to section 319 of the Public Health Service Act, that a public health emergency as a result confirmed cases of 2019 Novel Coronavirus, exists and has existed since January 27, 2020, nationwide.

3/13/2020	/s/
Date	Alex M. Azar II

345) 2020-03-14 Zhihuan L: China sending medical team to help Italy contain virus. ChinaDaily 14 March 2020: 1-2.

https://www.chinadaily.com.cn/a/202003/14/WS5e6bd352a31012821727f096.html

346) 2020-03-16 Brown BL, McCullough J: Treatment for emerging viruses: Convalescent plasma and COVID-19. Transfusion and Apheresis Science 59 (2020) 102790: 1-5. https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1.full.pdf

2020-04-14: accepted for publication:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194745/pdf/main.pdf

ABSTRACT

Use of convalescent plasma transfusions could be of great value in the current pandemic of coronavirus disease (COVID-19), given the lack of specific preventative and therapeutic options. This convalescent plasma therapy is of particular interest when a vaccine or specific

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therapy is not yet available for emerging viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. This report summarizes existing literature around convalescent plasma as a therapeutic option for COVID-19. It also includes recommendations for establishing a convalescent plasma program, enhancement considerations for convalescent plasma, and considerations around pathogen reduction treatment of convalescent plasma. Time is of the essence to set up protocols for collection, preparation, and administration of apheresis-collected convalescent plasma in response to the current pandemic. The immediate use of convalescent plasma provides prompt availability of a promising treatment while specific vaccines and treatments are evaluated and brought to scale. Further development of improved convalescent plasma, vaccines and other therapeutics depends on quick generation of additional data on pathogenesis and immune response. Additionally, given the lack of information around the natural history of this disease, PRT should be considered to add a layer of safety to protect recipients of convalescent plasma.

- 347) 2020-03-17 Azar A: Declaration under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19. Federal Register, 3/17/2020. https://www.federalregister.gov/documents/2020/03/17/2020-05484/declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical-countermeasures
- 348) 2020-03-17 Regeneron: Regeneron announces important advances in novel COVID-19 antibody program. https://investor.regeneron.com/news-releases/news-rele
- 349) 2020-03-18 Duan K, Liu Bende, Li Cesheng, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X: Effectiveness of convalescent plasma therapy in severe COVID-19 patients. 18 March 2020; PNAS (Proceedings of the National Academy of Sciences of the United States of America): 1-22. https://www.pnas.org/content/pnas/117/17/9490.full.pdf

Currently, there are no approved specific antiviral agents for novel coronavirus disease 2019 (COVID-19). In this study, 10 severe patients confirmed by real-time viral RNA test were enrolled prospectively. One dose of 200 mL of convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above 1:640 was transfused to the patients as an addition to maximal supportive care and antiviral agents. The primary endpoint was the safety of CP transfusion. The second endpoints were the improvement of clinical symptoms and laboratory parameters within 3 d after CP transfusion. The median time from onset of illness to CP transfusion was 16.5 d. After CP transfusion, the level of neutralizing antibody increased rapidly up to 1:640 in five cases, while that of the other four cases maintained at a high level (1:640). The clinical symptoms were significantly improved along with increase of oxyhemoglobin saturation within 3 d. Several parameters tended to improve as compared to pretransfusion, including increased lymphocyte counts (0.65 × 109 /L vs. 0.76 × 109 /L) and decreased C-reactive protein (55.98 mg/L vs. 18.13 mg/L). Radiological examinations showed varying degrees of absorption of lung lesions within 7 d. The viral load was undetectable after transfusion in seven patients who had previous viremia. No severe adverse effects were observed. This study showed CP therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases. The optimal dose and time point, as well as the clinical benefit of CP therapy, needs further investigation in larger well-controlled trials.

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- 350) 2020-03-18 Trump DJ: Declaring a national emergency concerning the novel coronavirus disease (COVID-19) outbreak.

 https://www.federalregister.gov/documents/2020/03/18/2020-05794/declaring-a-national-emergency-concerning-the-novel-coronavirus-disease-covid-19-outbreak
- **351)** 2020-03-18 Pharmaceutical Technology: Regeneron identifies several antibodies against Covid-19. https://www.pharmaceutical-technology.com/news/regeneron-covid-19-antibodies/
- 352) 2020-03-19 Adams J: PSA, If You Are Sick. March 19, 2020. https://www.facebook.com/WhiteHouse/videos/psa-if-you-are-sick/196091611816606/

As the Nation's doctor, I often get asked: What should I do if I think I might have coronavirus? Well, it is important to know the symptoms—they include: fever, cough, and shortness of breath. If you are having these symptoms or worry you might have coronavirus, please call your healthcare provider. We don't want you to go into the ER or the doctor's office without talking to them first because you might spread coronavirus to someone else. They will help you think through and learn how to react including figuring out where to go to get tested if necessary.

Dr. Jerome Adams, PSA, If You Are Sick, March 19, 2020.

This PSA makes the assumption that American's have an established PCP's whom they can call but that is not truth:

Fong M: Nearly 1 in 5 Americans haven't seen a doctor in over five years. Onlinedoctor April 14, 2021. https://www.onlinedoctor.com/nearly-1-in-5-americans-havent-seen-a-doctor-in-over-five-years/

CDC: Percentage of having a wellness visit in past 12 months for adults aged 18 and over, United States, 2019. CDC, Centers for Disease Control and Prevention, National Center for Health Statistics: Interactive Summary Health Statistics for Adults—2019.

https://wwwn.cdc.gov/NHISDataQueryTool/SHS adult/index.html

CDC: National Ambulatory Medical Care Survey: 2018 National Summary Tables https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2018-namcs-webtables-508.pdf

353) 2020-03-19 Simpson BW: COVID-19's stop-gap solution until vaccines and antivirals are ready. Global Health NOW, Johns Hopkins Bloomberg School of Public Health https://www.globalhealthnow.org/2020-03/covid-19s-stop-gap-solution-until-vaccines-and-antivirals-are-ready

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals **Prevention**: Active Immunization: Vaccines

How can plasma be useful against the novel coronavirus?

When you recover from many viral diseases, you have in your blood what are called neutralizing antibodies. These are antibodies that kill the virus. Once you recover, the plasma be taken from donors. It's very safe. It's the same thing as using a blood donation except they don't take the red blood cells, they take the liquid. They take the plasma. It is itself a drug...it can be used for prevention of infection for people who are being exposed or it could be used for therapy for those who are sick.

It's not a vaccine. Think about it as the administration of a protein, it's a liquid that is given to people that gives them immunity.

Right. Because the vaccine would provoke the recipient's antibodies. You'll have the antibodies, but they won't be your antibodies—though it'll do the same thing.

Right.

And if somebody is already sick, can the plasma help them? Yes, it can be used for prevention or a treatment.

This strategy is already being used in China?Yes, in fact, the Chinese sent 90 tons of plasma to Italy.

- 354) 2020-03-20 Zhou G, Chen S, Chen Z: Advances in COVID-19: the virus, the pathogenesis, and evidence-based control and therapeutic strategies. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7171433/pdf/11684 2020 Article 773.pdf
- 355) 2020-03-20 Healy M: How the blood of coronavirus survivors may protect others from COVID-19. Los Angeles Times 20 March 2020, 1/8. https://www.latimes.com/science/story/2020-03-20/how-blood-from-people-who-survived-covid-19
- 356) 2020-03-21 Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu Ch, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang QW, Xu SY, Zhu HD, Xu YC, Ji Q, Sharma L, Wang L, Wang J: Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clin Infect Dis XX XXXX 2020; XX: 1-8.

 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184472/pdf/ciaa310.pdf; Clin Infect Dis 2020 Jul 28; 71(15): 778-785. https://pubmed.ncbi.nlm.nih.gov/32198501/
- 357) 2020-03-23 Good/Shutterstock M: World Health Organization warns against untested drugs for COVID-19. Biospace https://www.biospace.com/article/world-health-organization-warns-against-untested-drugs-for-covid-19/
- 358) 2020-03-23 Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, *et. al.*: The feasibility of convalescent plasma therapy in severe COVID-19 patient: a pilot study. medRxiv Mar 23, 2020; 1 21. https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1.full.pdf
- 359) 2020-03-23 U.S. Food and Drug Adminstration: Emergency Use Authorization. Emergency Use Authorization (EUA) information, and list of all current EUAs.

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https://web.archive.org/web/20200324160355/https://www.fda.gov/emergency-preparednessand-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

- 2020-03-23 Bhandari T: Possible COVID-19 treatment: transfusion of antibodies from recovered patients' blood—Century-old idea applied to modern pandemic. https://medicine.wustl.edu/news/possible-covid-19-treatment-transfusion-of-antibodies-fromrecovered-patients-blood/
- 2020-03-24 Scrip Team: Coronavirus Update: South Korea's Celltrion progresses antibody, Yancopoulos: 'The World is Counting on Us' – Antibody Therapies could ease huge burden on emergency care. Informa Pharma Intelligence https://scrip.pharmaintelligence.informa.com/SC141901/Coronavirus-Update-South-Koreas-Celltrion-Progresses-Antibody-Yancopoulos-The-World-Is-Counting-On-Us

2020-03-24 U.S. Food and Drug Administration: **Investigational COVID-19 Convalescent Plasma – Emergency** INDs, March 24, 2020.

https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20 %20FDA.pdf

- · Eligible patients for use under expanded access provisions:
 - o Must have laboratory confirmed COVID-19
 - Must have severe or immediately life-threatening COVID-10 for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 5 % within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure
 - septic shock, and/or

27/3/2020 estigational COVID-19 Convalescent Plasma - Emergency INDs | FDA multiple organ dysfunction or failure Mast provide informed consent ¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus

Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

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NO WHERE in the aforementioned reference #1 by Wu and McGoogan upon which officially the U.S. FDA based the Eligibility Criteria for administration of COVID-19 Convalescent Plasma from March 24, 2020 to September 2, 2020 is "CONVALESCENT", "PLASMA", "ELIGIBILITY" or "CRITERIA" mentioned even once !!!!

2020-03-24 Investigational COVID-19 Convalescent Plasma – Emergency INDs. (This is the NATAP Verbatim internet copy of reference 28 in its entirety that I have copied and pasted verbatim to follow from https://natap.org/2020/COVID/032320 39.htm as this is an original copy I can find on the Internet which is of the FDA's directive of March 24, 2020 that directed all the *misdirection based on only one reference #1 by Zunyou Wu, M.D., PhD, Jennifer M. McGoogan, PhD which never mentions COVID-19 Convalescent Plasma nor recommends* the eligibility criteria justifying the FDA authorizations of COVID-19 Convalescent Plasma (CCP), and EUAs that were to follow in the next 10 months.)

PLEASE NOTE THAT WEB SITE REFERENCED JUST BELOW MARCH 24, 2020

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds IS A HYPERLINK THAT BECAUSE OF THE FDA OVERWRITING PRACTICES AS PERMITTED BY THAT WHICH WAS PUBLISHED IN THE FEDERAL REGISTER on March 25, 2020 now points ex post facto to the future FDA website: Recommendations for Investigational COVID-19 Convalescent Plasma, February 11, 2021, and then with each overwrite ad infinitum. (One can trace back the referenced website with modifications using the Internet Archive (Wayback Machine -- https://archive.org/web/) to April 8, 2020. The FDA version of the verbatim document below must have been referenced between March 24, 2020 to ~April 8, 2020 was electronically replaced so that media articles (listed below) referencing the March 24, 2020 announcement ex post facto references to April 8, 2020.

I. therefore, allege that there was Blantant Misdirection of the official FDA documentation of March 24, 2020 in which the Eligibility Criteria is wrongly attributed to reference #1 which initiated the administration of CCP TO ONLY EXTREMELY ILL INDIVIDUAL PATIENTS AT THE WRONG TIME (not during the early viremic phase or prophylactically) which was probably a Federal Criminal Offense by someone in the FDA, Department of Health and Human Services, and/or The White House.

I allege, on behalf of the American people, this <u>misdirection of official federal FDA</u> documentation facilitated: 1) misdirected CCP application at an inappropriate (wrong) <u>late-in-time</u> in the course of the disease in >700,000 individuals having contracted COVID-19 and having developed life-threatening systemic complications (e.g., bilateral pneumonitis, kidney failure, etc.; 2) promoted nonsensical, inappropriate medical research/NIH ClinicalTrials (https://www.clinicaltrials.gov/ of CCP at the wrong administration time); 3) promoted violation of PL-115-176--*The Right to Try Law*-by promoting NON Completion of Phase I Studies; 4) promoted CCP application late in the individual's COVID-19 disease (which is the WRONG TIME to administer *Passive Immunization*); 5) led to the *de facto* discrediting of *Passive Immunization* as a <u>treatment</u>; 6) promoted *de facto* physician abandonment of their individual COVID-19 positive patients early in the course of the individual's disease (viremic phase); and 7) inadvertently led to greater than a half-of-a-million American deaths!

Below, copied and pasted *verbatim* from the National AIDS Treatment Advocacy Project (NATAP) https://natap.org/2020/COVID/032320_39.htm is the <u>original NATAP copy</u> found of the FDA's directive of March 24, 2020 that directed the *misdirection* regarding the eligibility criteria, FDA authorizations of COVID-19 Convalescent Plasma (CCP), and EUAs that were to follow for the next 10 months.

Investigational COVID-19 Convalescent Plasma - Emergency INDs

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March 24, 2020

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from public health threats including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to doing everything we can to provide timely response efforts to this pandemic and facilitate access to investigational drugs for use in patients with serious or immediately life-threatening COVID-19 infections.

One investigational treatment being explored for COVID-19 involves the use of convalescent plasma collected from recovered COVID-19 patients. It is possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. Although promising, convalescent plasma has not been shown to be effective in every disease studied. It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so. Investigators wishing to study the use of convalescent plasma are encouraged to submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).

Although participation in clinical trials is one way for patients to obtain access to convalescent plasma, these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the expanding COVID-19 outbreak presents, while clinical trials are being conducted, FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency Investigational New Drug Applications (eINDs) for Individual patients under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This does not include the use of COVID-19 convalescent plasma for the prevention of infection.

Healthcare providers interested in the emergency use of investigational COVID-19 convalescent plasma under a single patient emergency IND should consider the following:

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COVID 19 Convalescent Plasma

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Additional considerations for donor eligibility should be addressed, as follows:

- · Prior diagnosis of COVID-19 documented by a laboratory test
- · Complete resolution of symptoms at least 14 days prior to donation
- . Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at https://www.fda.gov/medical-devices/emergency-
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug-Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

- Eligible patients for use under expanded access provisions:
 - Must have laboratory confirmed COVID-19
 - Must have severe or immediately life-threatening COVID-19 for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial exygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 Life-threatening disease is defined as:
 - - respiratory failure,
 - septic shock, and/o
 - multiple organ dy function or failure
 - Must provide informed consent

How to obtain authorization for use of COVID-19 convalescent plasma

- For request that are not highly time sensitive (response from FDA provided within 4 to 8 hours), the requesting physician may contact FDA by completing form 3926 (https://www.fda.gov/media/98616/download) and submitting the form by email to CBEF
 - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesing the proposed investigational treatment in order to meet the expanded access use requirements of 21 CFP 312.305 and 312.310.

 The form should include information regarding where the COVID-19 convalescent plasma will be obtained.

 - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required
- FDA will review the request and, upon approval, FDA will send the requesting physician a confirmatory email that includes the emergency IND number.

 In the event of an emergency that is highly time sensitive (response required in less than 4 hours) or where the provider is unable to complete and submit form 3926 due to extenuating circumstances, the provider may contact FDA's Office of Emerger cy Operations at 1-866-300-4374 to seek verbal authorization.
 - o If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 1 working days of FDA's authorization of the use.

In addition to the above JOA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers or Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

¹ Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Content current as of: 03/24/2020

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Mr. President:

The article of Wu Z, McGoogan JM: Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 from the Chinese Center for Disease Control and Prevention IS AN EPIDEMIOLOGY REPORT which NEVER SPEAKS OF THERAPY. - The U.S. FDA, NIH, CDC, PHS, ORGANIZED, ACADEMIC, AND RESEARCH MEDICINE, etc. MISINTERPRETED this article and APPLIED IT **WRONGLY!**

-- THE TIMELY LATE ADMINISTRATION OF COVID-19 CONVALESCENT PLASMA AND the antiviral REMDESIVIR became a de facto faulty, tragic, DEADLY rationing METHODOLOGY late in the disease of COVID-19 DURING THE CYTOKINE CASCADE AND THE BRADYKININ STORM INSTEAD OF WITHIN <72-120 HOURS OF EARLY VIREMIA FROM THE INITIAL DOCUMENTATION by testing OF AN INDIVIDUAL'S INFECTION AND/OR INITIATION OF SYMPTOMATOLOGY. This U.S. governmental directive by edict regarding ADMINISTRATIVE TIMING OF COVID-19 Convalescent Plasma Therapy and the antiviral Remdesevir WAS ABSOLUTELY LATE and DEADLY WRONG; and it has been contributory in > 1 million deaths from COVID-19 in the U.S.A. over the last two years!

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- 363) 2020-03-24 FDA: Investigational COVID-19 Convalescent Plasma Emergency INDs. "A licensed physician must request the Emergency IND (eIND) and obtain the COVID-19 convalescent plasma from a blood center. FDA does **not** provide COVID-19 convalescent plasma for eINDs. Investigational COVID-19 Convalescent Plasma Emergency INDs Frequently Asked Questions (/media/136470/download). [this download now points to: https://www.fda.gov/media/136470/download which is April 3, 2020.].
- 364) 2020-03-24 U.S. Food and Drug Administration: FDA NEWS RELEASE: Coronavirus (COVID-19) Update: Daily Roundup, March 24, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-24-2020
- 365) 2020-03-24 Global Biodefense Staff: FDA allows emergency used of investigational convalescent plasma for critical COVID-19 patients.

 https://globalbiodefense.com/2020/03/24/fda-allows-emergency-use-of-investigational-convalescent-plasma-for-critical-covid-19-patients/
- 366) 2020-03-24 Desperate for Covid-19 answers, U.S. doctors turn to colleagues in China. STATnews. https://www.statnews.com/2020/03/24/covid-19-answers-doctors-turn-to-china/
- 367) 2020-03-24 Palca J: FDA Expedites Treatment of Serious III COVID-19 Patients with Experimental Plasma. NPR, March 24, 2020. https://www.npr.org/sections/coronavirus-live-updates/2020/03/24/820939536/fda-expedites-treatment-of-seriously-ill-covid-19-patients-with-experimental-pla
- 368) 2020-03-24 Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, Chen Q, Zhang L, Zhong Q, Zhang X, Zou Y, Zhang S: Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. Chest 24 March 2020: e1-e5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7195335/pdf/main.pdf
- 369) 2020-03-24 Osborne H: What is convalescent plasma? New York health officials to start trial using blood of people recovered from coronavirus. Newsweek. 24 March 2020: 1-23. https://www.newsweek.com/what-convalescent-plasma-new-york-health-officials-start-trial-using-blood-people-recovered-1493964
- 370) 2020-03-25 DEPARTMENT OF HEALTH AND HUMAN SERVICES, Food and Drug Administration: Federal Register / Vol. 85, No. 58 / Wednesday, March 25, 2020 / Notices. 16949-16950. https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf
- 371) 2020-03-25 U.S. Food and Drug Adminstration: Emergency Use Authorization. Emergency Use Authorization (EUA) information, and list of all current EUAs. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

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- 2020-03-25 Regional Platform on Access and Innovation for Health Technologies_{PRAIS}, Pan American Health Organization, World Health Organization: FDA: Investigational COVID-19 Convalescent Plasma – Emergency Investigational New Drug Applications, March 25, 2020. https://prais.paho.org/en/fda-investigational-covid-19-convalescent-plasmaemergency-investigational-new-drug-applications/
- 2020-03-26 Hopkins Tanne J: Covid-19: FDA approves use of convalescent plasma to 373) treat critically ill patients. BMJ 2020; 368:m1256 doi: 10.1136bmj.m1256 (Published 26 March 2020). https://www.bmj.com/content/bmj/368/bmj.m1256.full.pdf

Dear Mr. President: I apologize for copying and pasting the following excerpted as this is copyright protected material by the BMJ Publishing Group Limited but I am presenting this to you as Educational Material BUT the URL to which the references point were changed by the FDA so that the eligible criteria justifying reference "1" of March 24, 2020 is extremely difficult to find: Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. –C. Andrus, M.D.

Plasma from people who have recovered from covid-19 may contain antibodies to the virus that causes the disease and might be effective against the infection, the FDA said. Convalescent plasma has been studied in outbreaks of other respiratory infections, such as H1N1 influenza, SARS, and MERS. "Although promising, convalescent plasma has not been shown to be effective in every disease studied" and therefore clinical trials were needed to see if it was useful in covid-19, the FDA cautioned.

The FDA told doctors wanting to study the use of convalescent plasma to follow the usual system for an investigational new drug (IND) application.

The plasma must be collected from recovered patients who can donate blood, have had no symptoms for 14 days, and have had negative results on covid-19 tests.

However, given the current public health emergency, the FDA said it was providing emergency access to convalescent plasma for patients "with serious or immediately life threatening covid-19 infections."

Severe disease is defined as dyspnoea, respiratory frequency ≥30 breaths per minute, blood oxygen saturation ≤93%, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2 /FiO2) 50% within 24 to 48 hours.

Life threatening disease is defined as respiratory failure, septic shock, or multiple organ dysfunction or failure. In such cases, doctors can submit a form online or call FDA's hotline telephone number (1-866-300-4374) to get verbal approval for treatment, which is promised within four to eight hours.

Jeffrey Henderson of Washington University School of Medicine in St Louis, Missouri, told National Public Radio, "The FDA just opened the floodgates. Our institution is scrambling to be ready to use this. There are many others, I'm sure." 3

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- 1 FDA. Investigational covid-19 convalescent plasma—emergency INDs, https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ideprocess-cber/investigational-covid-19-convalescent-plasma-emergency-inds
- 2 Hixenbaugh M. FDA will allow doctors to treat critically ill coronavirus patients with blood from survivors. NBC News 2020 Mar 24. www.nbcnews.com/news/us-news/fda-will-allowdoctors-treat-critically-ill-coronavirus-patients-blood-n1167831
- 3 Palca J. FDA expedites treatment of seriously ill covid-19 patients with experimental plasma. National Public Radio, 24 Mar 2020. www.npr.org/sections/coronavirus-liveupdates/2020/03/24/820939536/fda-expedite-treatment-of-seriously-ill-covid-19-patientswith-experimental-plasma

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374) 2020-03-27. Hinton DM: From the EUA update 091 of July 30, 2021. https://www.regeneron.com/downloads/treatment-covid19-eua-fda-letter.pdf https://www.fda.gov/media/145610/download

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19). ¹ On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.²

- 375) 2020-03-27 Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L: Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020 Apr 28;323 (16): 1582-1589. https://jamanetwork.com/journals/jama/fullarticle/2763983
- 376) 2020-03-27 Roback JD, Guarner J: Convalescent plasma to treat COVID-19, Possibilities and challenges. JAMA 2020; 323(16): 1561-1562. https://jamanetwork.com/journals/jama/fullarticle/2763982
- 377) 2020-03-28 Brunk D: FDA Oks emergency use of convalescent plasma for seriously ill COVID-19 patients. Medscape Medical News. March 28, 2020. https://www.medscape.com/viewarticle/927716
- 378) 2020-03-29 U.S. Food and Drug Adminstration: Emergency Use Authorization. Emergency Use Authorization (EUA) information, and list of all current EUAs. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
- 379) 2020-03-30 U.S. Department of Health & Human Services, Centers for Medicare and Medicaid Services: Center for clinical standards and quality/quality, safety and oversight group. Ref: QSO-20-15 Hospital/CAH/EMTALA REVISED.

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https://web.archive.org/web/20200413235000if_/https://www.cms.gov/files/document/qso-20-15-hospital-cah-emtala-revised.pdf

- **380)** 2020-03-30 ACEP COVID-19 Field Guide: EMTALA Regulations and Liability. https://www.acep.org/corona/covid-19-field-guide/regulations-and-liability/emtala/
- 381) 2020-03-30 Roos D: Before vaccines, doctors 'borrowed' antibodies from recovered patients to save lives –Doctors first tried injecting patients with blood plasma in the early 1900s. The method has been used against diphtheria, the 1918 flu pandemic, measles and Ebola. History Channel Updated Apr 1, 2020. https://www.history.com/news/blood-plasma-covid-19-measles-spanish-flu
- **382)** 2020-03-31 U.S. Food and Drug Administration: Emergency Use Authorization. https://web.archive.org/web/20200331212526/https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
- 383) 2020-04-01 Weise E, Johnson M: The first US coronavirus patients are being treated with convalescent plasma therapy. Will it work? Not even the doctors know. USA Today 1 Apr 2020: 1-5. https://www.usatoday.com/story/news/health/2020/04/01/coronavirus-plasma-therapy-5-us-patients-covid-19-donors/5090946002/
- 384) 2020-04 Chen L, Xiong J, Bao L, Shi Y: Convalescent plasma as a potential therapy for COVID-19. The Lancet 2020 April; 20: 398-400. https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30141-9.pdf
- 385) 2020-04-01 O'Donnell N: BREAKING NEWS: Dr. Fauci on the fight against the virus. https://www.facebook.com/CBSEveningNews/videos/norah-odonnell-should-we-be-advising-people-to-wear-masksdr-anthony-fauci-great-/204826050813336/ 2:10 2:48

Norah O'Donnell: With all due respect it does seem like so much of this we're making it up as we go along.

Dr. Anthony Fauci: Well, you know you make it up as you go along, Norah, because that's what you know—that's where the war is all about. I don't like to necessarily make that analogy to a war, but if you talk to the generals with experience, you have a plan. But when the bullets start flying, everything becomes a fog, and you have to play it by ear. We do have a good plan. We need to be humble that we don't know all the answers, and we don't know how exactly this is going to turn out.

Norah O'Donnell: Dr. Fauci, thank you so very much for your time and expertise.

Dr. Anthony Fauci: It's always good to be with you, Norah. Thank you.

386) 2020-04-02. Cerus: Cerus Corporation announces the inclusion of pathogen reduction technology in the ISBT working party recommendations for the preparation of COVID-19 convalescent plasma. BioSpace https://www.biospace.com/article/releases/cerus-

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- corporation-announces-the-inclusion-of-pathogen-reduction-technology-in-the-isbt-workingparty-recommendations-for-the-preparation-of-covid-19-convalescent-plasma/
- 387) 2020-04-02 McCarthy A: Could plasma from recovered COVID-19 patients help others? Boston Children's Hospital. https://answers.childrenshospital.org/covid-19-coronavirusplasma/
- 2020-04-03. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JWM, Brüggermann RJ, van der Hoeven H: Kinins and cytokines in COVID-19: a comprehensive pathophysiological approach. Pre Prints: Posted Not PEER-reviewed. https://www.preprints.org/manuscript/202004.0023/v1
- 389) 2020-04-03 Langhi Junior DM, De Santis GC, Bordin JO: COVID-19 convalescent plasma transfusion. ABHH: Associação Brasileira de Hematologia, Hemoterapio e Teopia Celular 3 April 2020: 113-115. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164882/pdf/main.pdf
- 2020-04-03 FDA: Investigational COVID-19 convalescent plasma Emergency INDs, Frequently Asked Questions. FDA, 3 April 2020. https://www.fda.gov/media/136470/download
- 391) 2020-04-03 Mogensen JF: Can COVID-19 be treated? Does blood from survivors help? Experts answer our questions on antibodies. Mother Jones, 1-5. https://www.motherjones.com/politics/2020/04/coronavirus-covid-survivors-treatmentsconvalescent-plasma-answers/
- **392)** 2020-04-03 Centers for Disease Control and Prevention: Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19. (CDC recommendation started January 31, 2020 to present with last overwriting update feb 16, 2021. http://web.archive.org/web/20200408110417/https://www.cdc.gov/coronavirus/2019ncov/hcp/clinical-guidance-management-patients.html
- 393) 2020-04-04 Joyner M, (Principal Investigator): COVID-19 expanded access program --Convalescent Plasma COVID-19 (coronavirus) Treatment – Mayo Clinic. First date digitally preserved by the Internet Archive (Wayback Machine). -Origin of the FDA/Mayo Clinic expanded access program. (Compassionate Use—can't be used for Randomized Controlled Trials by definition of the NIH and FDA) https://web.archive.org/web/20200404010134/https://www.uscovidplasma.org/

The protocol requires the patient or family member to consent to receiving plasma from someone who has recovered from COVID-19. Their plasma has substances that could improve chances of recovery. Only hospitalized patients referred by their health care provider will participate in this protocol.

Hospitalized patients are eligible to receive convalescent plasma if:

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- They are 18+ years of age
- They have laboratory-confirmed diagnosis of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19
- They are admitted to an acute care facility for the treatment of COVID-19 complications
- They have severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
- There is informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:

- Shortness of breath (dyspnea)
- Respiratory frequency ≥ 30/min
- Blood oxygen saturation ≤ 93%
- Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- Lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:

- Respiratory failure
- Septic shock
- Multiple organ dysfunction or failure

Michael J. Joyner, M.D., Summary, Mayo Clinic. https://www.mayo.edu/research/faculty/joyner-michael-j-m-d/bio-00078027

- 394) 2020-04-04 O'Donnell R: Before Dr. Anthony Fauci was the leading Covid-19 expert, he was captain of his high school basketball team. SBNATION https://www.sbnation.com/nba/2020/4/4/21207982/dr-anthony-fauci-coronavirus-covid-19-expert-high-school-basketball-team
- 395) 2020-04-06 Xinhua: Timeline of China releasing information on COVID-19 and advancing international cooperation. ChinaDaily, 6 April 2020: 1-3. https://www.chinadaily.com.cn/a/202004/06/WS5e8b2f5aa31012821728496b.html
- 396) 2020-04-06 Ledger K: Convalescent plasma: A therapy for COVID-19. Discovery's Edge—Mayo Clinic's Research Magazine 6 April 2020: 1-4. https://discoverysedge.mayo.edu/2020/04/06/convalescent-plasma-a-therapy-for-covid-19/
- 397) 2020-04-06 CSL Behring: Global plasma leaders collaborate to accelerate development of potential COVID-19 hyperimmune therapy. 6 April 2020: 1-6. https://www.cslbehring.com/newsroom/2020/covid-19-hyperimmune (Kennedy DB, Vice

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals **Prevention:** Active Immunization: Vaccines

President – North America Medical Affairs: A letter from CSL Behring, form-letter email 6 April 2020: 1-2).

398) 2020-04-07 Bloch EM, Shoham S, Casadevall A, Sachals BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JR, A, Lau B, Wesolowski A, Katz L, Shan H, Auwaerter PG, Thomas D, Sullivan DJ, Paneth N, Gehrie E, Spitalnik S, Hod EA, Pollack L, Nicholson WT, Pirofski L, Bailey JA, Tobian AAR: Deployment of convalescent plasma for the prevention and treatment of COVID-19. https://www.jci.org/articles/view/138745

...Convalescent plasma has also been used in the COVID-19 pandemic; limited data from China suggest clinical benefit, including radiological resolution, reduction in viral loads, and improved survival....

- 399) 2020-04-07 Wu Z, McGoogan JM: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. Jama April 7, 2020; 323(13): 1239-1242. https://jamanetwork.com/journals/jama/fullarticle/2762130 (reference first released in Feb 2020, **ref. 326** above on 2020-02-24).
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- **401)** 2020-04-07 Rivera N: Medical Task Force COVID-19 (Puerto Rico): Investigational COVID-19 Convalescent Plasma Emergency Investigational New Drug, Date April 7, 2020. https://covid19tf.rcm.upr.edu/wp-content/uploads/sites/45/2020/04/Protocolo28-Convalescent-Plasma-1.pdf

Since only limited data exits at this moment regarding the effectiveness of this therapy, it cannot be routinely recommended or use as a proven treatment option. The Food and Drug Administration (FDA) has provided several pathways to administer or study the use of convalescent plasma in COVID-19 patients:

- Clinical Trials: Investigators wishing to study the use of convalescent plasma need to submit a request to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).
- Expanded Access: FDA is working with multiple federal partners and academia to open an expanded access protocol to facilitate access to COVID-19 convalescent plasma. For patients with, or at risk of, severe or life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials, access may be available through participation of acute care facilities in an investigational expanded access protocol under an IND already in place.
- Single Patient Emergency IND: For patents who are not able to participate in a clinical trial or in an expanded access program, given the public health emergency FDA also is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of the patient's physician requesting a single patient emergency Investigational New Drug Application (eINDs) for the individual patient under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This eIND process is not for the use of COVID-19 convalescent plasma for the prevention of infection.
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403) 2020-04-08 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. April 8, 2020.

https://web.archive.org/web/20200413010215/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol External Link Disclaimer. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - *shortness of breath (dyspnea),*
 - respiratory frequency $\geq 30/min$,
 - blood oxygen saturation $\leq 93\%$,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 300,
 - *lung infiltrates* > 50% within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- *Informed consent provided by the patient or healthcare proxy.*
- 404) 2020-04-08 FDA: Recommendations for Investigational COVID-19 Convalescent Plasma. https://web.archive.org/web/20200408215026/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma which hyperlinked on 4/8/2020 to that which follows on 4/14/2020.
- 405) 2020-04-08 Pharmabiz.com: Global plasma leaders collaborate to speed up development of potential COVID-19 hyperimmune therapy. Pharmabiz.com, Osaka, Japan, Wednesday, April 8, 2020. http://www.pharmabiz.com/PrintArticle.aspx?aid=122309&sid=2
- **406)** 2020-04-08 Spencer G: A promising COVID-19 treatment gets fast-tracked. Johns Hopkins University HUB 8 April 2020: 1-9. https://hub.jhu.edu/2020/04/08/arturo-casadevall-blood-sera-profile/
- **407)** 2020-04-11 Robson B: COVID-19 Coronavirus spike protein analysis for synthetic analysis for synthetic vaccines, a peptidomimetic antagonist, and therapeutic drugs, and analysis of a proposed achilles' heel conserved region to minimize probability of escape

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals **Prevention:** Active Immunization: Vaccines

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- 411) 2020-04-13 U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma – Guidance for Industry. The original version of this directive for the Industry was issued and labelled as April 2020. The initial version of April 2020 for the Industry published for the website on which this was published can no longer be found on the Internet and the Internet Archive's first capture was April 14, 2020 of the revision version of April 13, 2020:

https://web.archive.org/web/20200414181056/https://www.fda.gov/media/136798/download

Ongoing on official FDA website URL below has been overwritten many times and captured (132 captures) by the Internet Archive from 14 Apr 2020 to 11 Mar 2022 per the Wayback Machine of the Internet Archive is: https://www.fda.gov/media/136798/download

As I printed out the original version of this document that is labelled April 2020 (I assume sometime prior to April 13, 2020), I realized that original version cannot be found on the Internet. Therefore, I have scanned and attached here my personal copy of the following to be forever recorded in history as the Original FDA version of:

Investigational COVID-19 Convalescent Plasma

Guidance for Industry

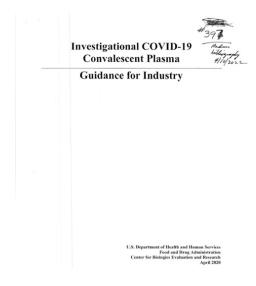
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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research April 2020

(As you will note, the FDA already had recognized its error of the FDA March 24, 2020, in that in its initial announcement of COVID-19 Convalescent Plasma as an Investigational drug the FDA had stipulated that COVID-19 Convalescent Plasma was to be given only to the very serious ill patients (late in the Cytokine Cascade and the Bradykinin Storm instead of early in the viremia) erroneously interpretating the Chinese epidemiology journal report³⁸⁵ regarding 72314 cases as a treatment directive (which it was not)!). As a lie of omission which went unnoticed, the FDA removed the late recommendations of administration from all its documentations regarding COVID-19 Convalescent Plasma beginning on September 2, 2020. Please compare eligibility critera for same FDA documents of reference 546 of September 1, 2020 versus 547 of September 2, 2020 that follow.—THE ELIGIBILITY REQUIREMENTS FOR LATE ADMINISTRATION WERE REMOVED BY SOMEONE IN THE FDA.



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Public Comment This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (TDA or Agency) has determined that prior public public benefit emergency. This guidance is being implemented without prior public comment hecause the Food and Drug Administration (TDA or Agency) pass determined that prior public public

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Investigational COVID-19 Convalescent Plasma

Guidance for Industry

is guidance represents the current thinking of the Food and Drug Administration (FDA or sency) on this topic. It does not establish any rights for any person and is not binding on FDA the public. You can use an alternative approach if it satisfies the requirements of the plicable statutes and regulations. To discuss an alternative approach, contact the FDA staff

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States (U.S.) from threats including emerging infectious diseases, such as the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalencent plasma collected from individuals who have recovered from CoVID-19 (cVOID-19 convalencent plasma) during the public health emergency. The guidance also provides recommendations to blood establishments on the collection of CVOID-19 (convalencent plasma).

The recommendations in this guidance are intended to remain in effect only for the duration of he public health emergency related to COVID-19 declared by the Department of Health and furnan Services (HHS), including any renewals made by the Secretary in accordance with ection 319(a)(2) of the Public Health Service Act (PHS Act).

Given this public health emergency, and as discussed in the Notice published in the Federal Register of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019", available at https://www.goviinfs.gov/content/pkg/FR-0202-03-25/eff/0202-03-222-pdf this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701/b/t) (1/0) of the Federal Food, Dung, and Cosmonic Act (FDAC Act) and Title 21 of the Code of Federal Regulations (CFR) 21 CFR 10.115(g/Z)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

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In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.3 In addition on March 13, 2020, the President declared a national emergency in response to COVID-19.

One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19 (Refs. 1-4). Convalescent plasma that contains antibodies to sever acute respiratory syndrome coronavirus 2 or SARS-COV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2005 SARS-CoV-1 epidemic (Refs. 5-7).

pandemic, and the 2012 MERS-CoV epidemic (Refs. 5-7).

Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials. This guidance provides recommendations to health care providers and investigations on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma other convalescent plasma) during the public health emergency. This guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

A. Pathways for Use of Investigational COVID-19 Convalescent Plasma

Because COVID-19 convalescent plasma has not yet been approved for use by FDA,³ it is regulated as an investigational product. As such, administration of COVID-19 convalescent plasma by a health care provider must be under an investigation mee wrus application (IND) under the traditional IND regulatory pathway, an expanded access IND, or a single-patient emergency investigational new drug application (eIND) (42

Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. Jan. 31, 2020. (Accessible at Higher/www.pho.gov/emergency/exess/beathsfusions/bel-Pages/2019-AGA/ areas.)
President Donald J. Temp, Preclamation on Deadraga y Salvoinal Emergency Concerning the Novel Coronavirus and Company of the Control of the Company of th

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

U.S.C. 262(a)(3); 21 U.S.C. 355(i); 21 CFR 601.21; and 21 CFR 312.1). FDA does not collect COVID-19 convalescent plasma or provide COVID-19 convalescent plasma. Collect COVID-19 convalescent plasma or provide COVID-19 convalescent plasma or provide COVID-19 convalescent plasma from an FDA-registered blood establishment.

The following pathways are available for administering or studying the use of COVID-19 convalescent plasma:

Investigators wishing to study the use of convalescent plasma in a clinical trial should submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR Part 312). CBER's Office of Blood Research and Review is committed to engaging with sponsors and reviewing such requests expeditiously.

An IND application for expanded access is an alternative for use of COVID-19 convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 CF8 31.2.05). F.DA has worked with multiple federal partners and academia to open an expanded access protocol to facilitate access to COVID-19 ovuelacent plasma across the nation. For patients with serious or immediately life-threatening COVID-19 who are not eligible for or who are unable to participate in randomized clinical trials, access to this investigational product may be available through participation of acute care facilities in an investigational expanded access protocol under an IND that is already in place. Currently, the following protocol is in place: National Expanded Access Treatment Protocol.

3. Single Patient Emergency IND

3. Single Patient Emergency IND
Although participation in clinical trials or an expanded access program are ways for patients to obtain access to convalescent plasma. For various reasons these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the COVID-19 pandemic presents, while clinical trials are being conducted and an expanded access protocol is available, FDA also is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of the patient's physician requesting a single patient (FDN) for the individual patient under 21 CFR 312.310. This process allows the use of an investigational drug for the terament of an individual patient by a licensed physician upone TDA authorization, if the applicable regulatory criteria are met. Note, in such case, a licensed physician seeking to administre COVID-19 convalescent plasma to an individual patient must request the clND (see 21 CFR 312.310(b)).

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a. To Obtain a Single Patient Emergency IND

To obtain a single patient eIND, the provider must determine that the probable on from the investigational drug is not greater than the probable risk from the disease or condition 21 CFR 312.310(a).

- For requests between 8am EST and 8pm EST (Mon-8un), the requesting physician may contact FDA by completing Form FDA 3926 (https://www.fda.gov/media/98616/download) and submitting the form by email to CEBR CHDN Covid-19aFDA.HHS.gov. For einDT requests submitted via email during this time frame, FDA will respond within 4 hours.
 - The completed form should include a brief clinical history of the
 patient, including: diagnosis, current therapy, and rationale for
 requesting the proposed investigational treatment in order to meet the
 expanded access use requirements in 21 CFR 312.305 and 21 CFR
 312.310.
 - o The form should include information regarding where the COVID-19 convalescent plasma will be obtained
 - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required. Providers are strongly encouraged to fill out the form electronically whenever possible.
 - FDA will review the request and, upon authorization, send the requesting physician a confirmatory email that includes the emergency IND number.
- · For requests between 8am EST and 8pm EST where the provider is unable to complete and submit Form 3926 due to extenuating circumstances, the provider can contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization
- For requests that are overnight between 8pm EST and 8am EST, the provider should contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
 - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., Form FDA 3926) within 15

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working days of FDA's authorization of the use (21 CFR 312.310(d)(2)).

B. Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol, discussed in section III.A. of this guidance. These criteria include:

- · Laboratory confirmed COVID-19
- · Severe or immediately life-threatening COVID-19, for example,
- Severe disease is defined as one or more of the following:

 - shortness of breath (dyspnea),
 respiratory frequency 2 30/min,
 blood oxygen saturation 2 93%,
 partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 300
 - 300,
 lung infiltrates > 50% within 24 to 48 hours
- Life-threatening disease is defined as one or more of the following:
 respiratory failure,
 septic shock,
 multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

C. Collection of COVID-19 Convalescent Plasma

Under FDA's IND regulations, an IND (including an expanded access or eIND) must provide information with respect to the investigational drug, chemistry, manufacturing, and controls that is adequate to ensure the proper identification, quality, purity, and strength of the investigational drug (21 CRS 312-336/J7) and 21 CFR 312-305(b)(2)(ci)). For INDs for use of COVID-19 convalescent plasma, the IND would herefore need to contain, among other things, adequate information to demonstrate that the plasma will contain defined SARS-CoV-2 neutralizing antibody titers. Accordingly, health care providers or acute care facilities seeking to use COVID-19 convalescent plasma will be obtained from an I'DA-registered blood establishment that follows the donor eligibility criteria and donor qualifications described in section III.C.1. of this guidance in collecting plasma from donors.

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Donor Eligibility

- COVID-19 convalescent plasma must only be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15). Note the additional donor eligibility requirements for the collection of plasma by plasmapheresis in 21 CFR 630.15(b). Donation testing for relevant transhitsion-transmitted infections must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).
- b. COVID-19 convalescent plasma is collected from individuals who meet the following qualifications:
 - Evidence of COVID-19 documented by a laboratory test <u>either</u> by:
 - 1. A diagnostic test (e.g., nasopharyngeal swab) at the time of illness

- a positive serological test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID-19 was suspected.
- · Either one of the following:
- Complete resolution of symptoms at least 28 days prior to donation

Complete resolution of symptoms at least 14 days prior to donation, AND

Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.

- Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.
- · Defined SARS-CoV-2 neutralizing antibody titers
 - We recommend neutralizing antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

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 NOTE: If neutralizing antibody titers cannot be obtained in advance, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date.

Registered and licensed blood establishments that collect plasma intended for transfusion do not need to request a supplement to their license or obtain their own IND to collect and manufacture COVID-19 convalescent plasma for investigational use provided they 1) follow their standard operating procedures for plasma collection and all applicable regulation, and 2) collect plasma from individuals that meet the donor qualifications specified above, which would be included in the applicable IND(s) held by a health care provider or other sponsor.

Once manufactured, the COVID-19 convalescent plasma may be distributed for investigational use.

Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.120(a) to collect COVID-19 convalescent plasma.

Labeline

 The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use" (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.

- FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.
- b. We recommend the use of a uniform container label for COVID-19 convalescent plasma. In particular, we recommend the use of the International Society of Blood Transfusion (ISBT) format specified in the United States industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128.
- c. The manufacturing process used and the expiration date on the label for COVID-19 convalescent plasma should be the same as for other plasma products that are of the same type. For example, COVID-19 Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection,

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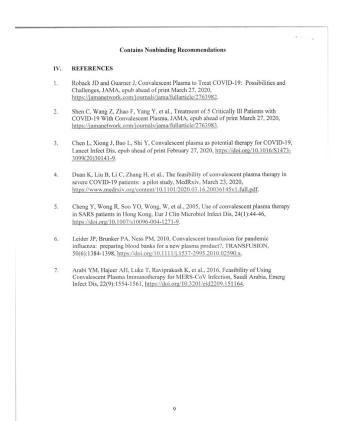
stored at -18C or colder and have an expiration date one year from the date of collection.

D. Recordkeeping

A health care provider who is participating in an IND, including an expanded access IND or elNID, must maintain records for the COVID-19 convalescent plasma unit(s) administered to the COVID-19 patient (2) CTRS 31.26.2). Such records should include the unique identification number(s) (e.g., the ISBT donation identification number(s)) of the unit(s).

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals



- 2020-04-13 Gibson Dunn: FDA round-up: Overview of emergency actions to expedite the availability of medical products to combat COVID-19, April 13, 2020. https://www.gibsondunn.com/wp-content/uploads/2020/04/fda-round-up-overview-ofemergency-actions-to-expedite-the-availability-of-medical-products-to-combat-covid-19.pdf Pages 14 – 15.
 - i. There are no FDA-approved drugs or vaccines to treat or cure COVID-19, but at the end of March, FDA launched the Coronavirus Treatment Acceleration Program (CTAP), a special emergency program to expedite the development of COVID-19 therapies. The CTAP program is using "every tool at the agency's disposal" to provide "ultra-rapid, interactive input."[41] FDA has turned around reviews on COVID-19 development plans within 24 hours and completed reviews of single-patient expanded-access requests within three hours. FDA has redeployed medical and regulatory staff to serve on review teams dedicated to COVID-19 therapies. FDA also has streamlined the process for developers and physicians to contact FDA with inquiries and to submit requests for the emergency use of investigational products. FDA is prioritizing these requests based on factors such as the product's scientific merits and the stage of development. In addition to clinical studies, FDA is looking at real-world data sources to inform its evaluation of potential

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- therapies, and FDA is leveraging scientific information being generated in China, Italy, Japan, and South Korea.
- ii. According to FDA, there are currently 10 therapeutic agents in active trials and 15 therapeutic agents in planning stages, and the Agency will publish updates as these therapies progress through the development process. Examples of potential therapies and vaccines include the following:
 - 1.) Remdesivir. Remdesivir is an investigational broad-spectrum antiviral treatment, which was previously tested to treat diseases caused by other coronaviruses, such as Ebola. FDA has been working with Gilead Sciences, Inc. to expedite the clinical studies of remdesivir in adults diagnosed with COVID-19 and to permit the emergency use of the drug through an expanded access program. In March, Gilead began enrolling patients in two Phase 3, randomized, open-label, multicenter clinical studies. One of the studies will evaluate the safety and efficacy of two dosing durations in addition to the standard of care for patients with severe COVID-19. The other study will evaluate the same dosing regimens in addition to the standard of care for patients with moderate COVID-19. Other ongoing studies of remdesivir include the NIAID Phase 2 adaptive, randomized, double-blind, placebo-controlled trial and studies in China and France.
 - 2.) Convalescent Plasma. Convalescent plasma, collected from individuals who have recovered from COVID-19, contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19). Use of convalescent plasma as a therapeutic agent has been studied in prior outbreaks of respiratory infections, such as the H1N1 influenza pandemic. Earlier this month, FDA entered a collaboration with BARDA, the American Red Cross, and the Mayo Clinic to simplify the process for health care providers to collect, distribute, and use convalescent plasma in patients. As a result of this collaboration, FDA estimates that thousands of units of plasma will be available to patients within the coming weeks. FDA also is working with NIAID to coordinate a study of hyperimmune globulin, which is a biological product manufactured from convalescent plasma.
- iii. On April 8, 2020, FDA issued guidance on the administration and study of investigational convalescent plasma during the public health emergency. [42] Prior to this guidance, FDA had approved emergency INDs for the use of convalescent plasma in very ill COVID-19 patients. The guidance provides recommendations regarding the regulatory pathways for using investigational COVID-19 convalescent plasma, patient eligibility, the collection of COVID-19 convalescent plasma from donors, labeling, and recordkeeping. In addition to the traditional IND pathway (21 C.F.R. Part 312), convalescent plasma may be permitted for investigational use through an expanded access IND for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 C.F.R. § 312.305) or through single patient emergency INDs following the request by a licensed physician (21 C.F.R. § 312.310). The convalescent plasma should be obtained from an FDA-registered blood establishment that follows the donor eligibility criteria and donor qualifications. Donors should have complete resolution of symptoms at least 28 days prior to donation or complete resolution of symptoms at least 14 days prior to donation and negative COVID-19 test results. FDA is relaxing requirements relating to the registration, licensure, and procedures of blood establishments that collect and distribute the convalescent plasma for investigational use.

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- 414) 2020-04-14 FDA first document of Guidance for industry. [U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma Guidance for Industry] https://web.archive.org/web/20200414181056/https://www.fda.gov/media/136798/download
- 415) 2020-04-14 Pardo J, Shukia AM, Chamarthi G, Gupte A: The journey of remdesivir: from Ebola and COVID-19. Drugs in Context 2020 Apr 14; 9: 1-9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7250494/pdf/dic-2020-4-14.pdf
- **416)** 2020-04-16 Komaroff AL: Reviewing Duan K *et al Proc Natl Acad Sci USA 2020 Apr 6*: Convalescent plasma therapy in patients with severe COVID-19. NEJM Journal Watch 16 April 2020: 5-6. https://www.jwatch.org/na51335/2020/04/16/convalescent-plasma-therapy-patients-with-severe-covid-19.
- 417) 2020-04-16 Cox D: The blood of coronavirus survivors could help tackle the pandemic. Wired, Wight Hosting, April 16, 2020. https://www.wired.co.uk/article/coronavirus-blood-plasma-trials
- 418) 2020-04-16. Wired, News Archives UK: The blood of coronavirus survivors could help cope with the pandemic. https://www.wired.co.uk/article/coronavirus-blood-plasma-trials
 The following was copied verbatim for documentation at the time of how China stopped there COVID-19 epidemic:
 - i. In late January, hospitals across China began using convalescent plasma as a treatment for Covid-19, and in recent weeks other countries have followed suit after the publication of initial results from Wuhan and Shanghai. While these trials involved just a small handful of patients, they received global attention as they appeared to demonstrate that convalescent plasma could aid recovery in even the most critically ill patients.
 - ii. "This is amazing because the vast majority of people thought that convalescent plasma could only be effective if administered early in the disease course," says Daniele Focosi, a transfusion specialist at Pisa University Hospital in Italy. "But the Chinese case series has proved clinical benefit even at a late stage which is very intriguing because it could be a life saving treatment."
 - iii. As of April 6, it was reported that 19 clinical trials of convalescent plasma are already taking place in China, the US, Italy, Iran, Mexico, and Colombia, with more planned. This week Italy is launching a nationwide initiative co-ordinated by Focosi's team at Pisa University Hospital which will use convalescent plasma in hospitals across five more of Italy's 20 regions, complementing an existing trial taking place in Lombardy, the epicentre of the Italian outbreak.

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- iv. In the UK, the NHS is currently seeking donors for two trials of its own which will compare convalescent plasma against other experimental medications such as antiviral drugs. "One of these trials is to treat patients with Covid-19 pneumonia who have not reached the stage of ventilation to try to stop that happening," says David Tappin, of the University of Glasgow School of Medicine, who is looking to obtain approval to run his own trial looking at whether convalescent plasma can help protect NHS workers. "The other is to treat severely ill patients already ventilated to try to reduce time on ventilators and to reduce death."
- v. But finding suitable donors is not as straightforward as it might seem. While there are more than 400,000 people around the world who have recovered from Covid-19, the rapid mutation rate of the virus as it has passed between countries means that donors have to be sourced locally. As the pandemic in Italy worsened last month, China reportedly offered to ship 90 tons of convalescent plasma to Italian hospitals for emergency use, but tests soon showed that it could not be used.
- vi. "We have evidence that the envelope protein called the spike protein is mutating," says Focosi, who is one of the co-investigators leading the new multi-centre trial in Italy. "So convalescent plasma collected in China may not be protective for Covid-19 patients in Europe and the US. You need antibodies derived from infection to the same strain which is circulating in your area."
- 419) 2020-04-17 Langi DM, Jr., De Santis GC, Bordin JO: Covid-19 convalescent plasma transfusion. Hematol Transfus Cell Ther. 2020 Apr-Jun; 42(2): 113 115. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164882/pdf/main.pdf
 - i. ... Therefore, all therapeutic options for the potentially lethal COVID-19 infection must be discussed ethically and scientifically. Historically, convalescent plasma (CP), a passive immunotherapy, has been used as a possible therapeutic option when no proven specific vaccine or drug is available for emerging infections.1,2 The administration of convalescent plasma or immunoglobulins has been shown to shorten the hospital stay and reduce the mortality rate in patients with SARS who did not respond to methylprednisolone in uncontrolled non-randomized clinical trials.3,4 Cheng et al. investigated 1775 SARS patients and found that 80 patients transfused with SARS convalescent plasma had a lower mortality rate, compared to non-transfused patients (12.5% vs. 17%).⁴
 - ii. Conclusions:
 - iii. Analogous to the SARS, the COVID-19 infection progresses with an intense inflammatory response that eventually causes serious lung damage, increasing the mortality risk. In the absence of a definitive curative management, many treatment algorithms have been explored in the treatment of the COVID19. Among possible interventions, the use of plasma collected from recovered patients shows an initial promise, however published results of rigorous clinical trials are needed before we may draw definitive effectiveness conclusions on this passive antibody therapy.
 - iv. The administration of the COVID-19 convalescent plasma must, however, fulfill some requirements related to availability of COVID-19 recovered donors: well-designed study protocols to guarantee the efficacy analysis of such an intervention; governmental and institutional compliance, and; laboratory support to perform serological and molecular assays, including the measurement of viral neutralization and immune response. In addition, the connection between hospitals, blood centers and the plasma industry must follow flawless strategies, as plasma units may be frozen before distribution or be manufactured as concentrated COVID-19 immunoglobulin.
- **420)** 2020-04-17 Gottlieb S: Former FDA chief Gottlieb explains the potential of Gilead's Covid-19 treatment. (The Antiviral Remdesivir)

 $\frac{https://www.cnbc.com/video/2020/04/17/gottlieb-treatment-gilead-clinical-trials-covid-19-squawk-box.html}{}$

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the last year and a half.].

- **421)** 2020-04-20 Cheen L, Xiong J, Bao L, Shi Y: Convalescent plasma as a potential therapy for COVID-19. www.thelancet.com/infection April 2020; 20: 398-400. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7128218/pdf/main.pdf
- 422) 2020-04-22 Fleming AB, Raabe V: Current studies of convalescent plasma therapy for COVID-19 may underestimate risk of antibody-dependent enhancement. J Clinical Virology 28 April 2020; 127: 104388.
 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7187833/pdf/main.pdf [While ADE (antibody dependent enhancement) is theoretically possible has been reported in the treatment of Dengue fever, it has not been observed or reported in the utilization of COVID-19 Convalescent Plasma in the thousands of patients that have received CCP in

...The first case series describing the use of convalescent plasma to treat critically-ill patients with COVID-19 showed clinical improvement and a decline in viral load in all treated patients, serving as a proof-on-concept for this strategy...

1. This shift may have a greater impact on disease severity if antibodies are present early in the course of infection. ...

Current studies of convalescent plasma are limited by lack of representation of patients in the early phase of infection, as well as confounding from multiple concurrent therapies and small patient numbers. ...

- **423)** 2020-04-23 Dzik S: COVID-19 Convalescent Plasma: Now is the time for better science. Transfusion Medicine Reviews 34 (2020141-144. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177063/pdf/main.pdf
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- 425) 2020-04-24 Trump D: Donald Trump Coronavirus press conference transcript April 24. Rev Apr 24, 2020. https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-april-24 The discussion of intravenous disinfectants overshadowed the conference in which Dr. Hahn mentioned Convalescent Plasma and other anti-viral therapies. BBC: Coronavirus: Outcry after Trump suggests injecting disinfectant as treatment. 24 April 2020. https://www.bbc.com/news/world-us-canada-52407177
- 426) 2020-04-27 van de Veerdonk FL, Netea MC, van Deuren M, van der Meer JWM, de Mast Q, Brüggemann RJ, van der Hoeven H: Kallikrein-kinin blockade in patients with COVID 19 to prevent acute respiratory distress syndrome. eLife 2020; 9 e57555. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7213974/pdf/elife-57555.pdf

- 427) 2020-04-28 Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X: Effectiveness of convalescent plasma therapy in severe COVID-19 patients. PNAS April 28, 2020; 117 (17): 9490-9496. https://www.pnas.org/content/pnas/117/17/9490.full.pdf
- **428)** 2020-04-28 Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP: The trinity of COVID-19: immunity, inflammation and intervention. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7187672/pdf/41577_2020_Article_311.pdf
- **429)** 2020-04-28 Zhu M, Hu K, Zhu Z: Use of convalescent plasma in COVID-19 patients in China. Transfusion Clinique et Biologique 28 April 2020: 1-2. https://www.em-consulte.com/showarticlefile/1367091/main.pdf
- **430)** 2020-04-28 NCR Editorial Staff: Editorial: Dolan delivers the church to Trump and the GOP. National Catholic Reporter Apr 28, 2020. https://www.ncronline.org/news/opinion/editorial-dolan-delivers-church-trump-and-gop
- **431)** 2020-04-29 Herper M, Feuerstein A: Critical study of Gilead's Covid-19 drug show patients are responding to treatment, NIH says. Statnews 29 Apr 2020: 1-8. https://www.statnews.com/2020/04/29/gilead-says-critical-study-of-covid-19-drug-shows-patients-are-responding-to-treatment/
- 432) 2020-04-29 Fung K: Dr. Fauci says remdesivir trial shows drug has promise as FDA plans to announce emergency use. Newsweek 29 Apr 2020: 1-10. https://www.newsweek.com/dr-fauci-says-remdesivir-trial-shows-drug-has-promise-fda-plans-announce-emergency-use-1501028
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Thus, our 3 severe patients were given convalescent plasma (50 ml, qod, twice) collected form 2 patients who had recovered from COVID-19. We detected SARS-CoV-2 antibodies (IgG and IgM) from the convalescent plasma of one donated patient using chemiluminescent immunoassay. The level of IgG was very high (>30 AU/ml) and 1gG (1:80) was 3,464 AU/mL. As expected, the level of IgM was very low (0.093 AU/mL). the CT images, blood gas analysis and symptoms improved the convalescent plasma transfusion. No adverse events were observed. One possible explanation for the efficacy of convalescent plasma is that the antibodies form convalescent plasma might suppress viraemia.²³

437) 2020-05-01 C-SPAN: President Trump Oval Office Remarks on Remdesivir. 2020 May 01. https://www.c-span.org/video/?471735-1/president-trump-oval-office-remarks-remdesivir

Mr. O'Day, Gilead Sciences CEO: What I'd like to say is that, you know, on behalf of Gilead, to the President's point, we feel a tremendous responsibility. We're humbled by this being an important first step for patients, for hospitalized patients. We want to make sure nothing gets in the way of these patients getting the medicine. So we made a decision to donate about 1.5 million vials of remdesivir.

- **438)** 2020-05-01 Sheridan C: Convalescent serum lines up as first-choice treatment for coronavirus. Nature Biotechnology 01 May 2020. https://www.nature.com/articles/d41587-020-00011-1
- **439)** 2020-05-01 U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma Guidance for Industry. https://web.archive.org/web/20200526150255/https://www.fda.gov/media/136798/download
- 440) 2020-05-01 Pérez-Cameo C, Marín-Lahoz J: Serosurveys and convalescent plasma in COVID-19. EClinicalMedicine 23 (2020) 100370. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7252163/pdf/main.pdf

The current pandemic is not only overwhelming the health systems of the affected countries but also is killing thousands of other ways healthy adults. Convalescent plasma has been proposed [1] and approved to treat COVID-19 based on the experience acquired treating other viral diseases such as influenza, Ebola, and SARS [2]. It is considered a safe treatment (at least its side effects and contraindications are well known) and it has proven to be efficacious in several viral infections for more than a century. Currently, several countries and health institutions are trying to gather convalescent sera for either empirical treatment or clinical trials. Based on the WHO interim guidance developed for the 2014 Ebola outbreak [3], convalescent plasma has advantages over other proposed treatment: it requires low technology (and therefore it can be produced where required independent of pharmaceutical companies), it is low cost and its production is easily scalable as long as there are sufficient donors.

441) 2020-05-01 Hinton D, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. (Initial EUA). https://web.archive.org/web/20200501204823/https://www.fda.gov/media/137564/download

Page 2:

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized remdesivir will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Gilead will supply remdesivir to authorized distributors⁴, or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;
- The remdesivir covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as SpO2 ≤ 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO); (The mechanism of remdesivir "...acts as a nucleoside analog and inhibits RNA-dependent RNA polymerase (RdRp) of coronaviruses...". Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, Farnung L, Siewert A, Hobartner C, Cramer P: Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nature Communications (2021)12:279 https://doi.org/10.1038/s41467-020-20542-0. https://www.nature.com/articles/s41467-020-20542-0.pdf Thus, the administration of remdesivir should be given early during the viral replication phase (best in <72 hours from diagnosis) rather than late in the symptomatology of COVID-19 cytokine storm and bradykinin increase.)
- Remdesivir is administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider; and
- The use of remdesivir covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.
- **442)** 2020-05-01 FDA: Recommendations for Investigational COVID-19 | FDA 1 May 2020: 1-6. http://web.archive.org/web/20200502165610/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
- 443) 2020-05-01 U.S. Department of Veterans Affairs, VA Pharmacy Benefits Management Services: Remdesivir emergency use authorization (EUA) Requirements, May 2020. https://www.va.gov/covidtraining/docs/20200618_Dynamic_Drugs_in_the_Battle_of_COVID_19/Remdesivir_Emergency_Use_Authorization_Requirements.pdf

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals **Prevention:** Active Immunization: Vaccines

<u>INCLUSION CRITERIA</u> (The patient must meet all these criteria. All answers must be <u>YES</u> to receive agent).

Patient is hospitalized with laboratory confirmed COVID-19 diagnosis

YES NO

The patient meets at least one of the following: need for mechanical ventilation, extracorporeal membrane oxygenation (ECMO), supplemental oxygen, or room air O₂ saturation ≤94% YES NO

Counseling provided and documented in the electronic health record as per EUA ** YES NO

- **The provider has communicated with the patient/caregiver information consistent with the "<u>Fact Sheet for Patients and Patients/Caregivers</u>" prior to the patient/caregiver information has been given the Fact sheet, informed that remdesivir is an unapproved drug authorized for use under EUA, given information on alternatives and their risks and benefits, and the patient/caregiver has the right to refuse or accept
- 444) 2020-05-02 Dowdy D, D'Souza G: Early herd immunity against COVID-19: A dangerous misconception. Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/from-our-experts/early-herd-immunity-against-covid-19-adangerous-misconception
- 445) 2020-05-02 U.S. FDA: Fact sheet for health care providers emergency use authorization (EUA) of Remesivir. (GS-5734TM) https://web.archive.org/web/20200502180648/https://www.fda.gov/media/137566/download
 - The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO2) \leq 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).
- 446) 2020-05-02 FDA: Fact Sheet for Health Care Providers Emergency Use AuthoriU.S. Department of Veterans Affairs, Veterans Health Administration.: Remdesivir FAQ https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/FAQ%20SHEETS/Remdesivir%20FAQ%20May%202020%20.docx No URL has been captured for this domain.
- 447) 2020-05-02 Roche JA, Roche R: A hypothesized role for dysregulated bradykinin signaling in COVID-19 respiratory complications. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7267506/pdf/FSB2-9999-na.pdf
- 448) 2020-05-03 Fitzgerald M: Gilead CEO says remdesivir will be available to patients this week: 'We've donated the entire supply.' CNBC 3 May 2020: 1-7. https://www.cnbc.com/2020/05/03/gilead-ceo-says-remdesivir-available-to-coronavirus-patients-this-week-weve-donated-the-entire-supply.html
- 449) 2020-05-03 Brennan M, O'Day: Transcript: Daniel O'Day discusses coronavirus treatment on "Face the Nation," May 3, 2020. CBS Face the Nation.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

https://www.cbsnews.com/news/transcript-daniel-oday-discusses-coronavirus-treatment-on-face-the-nation-may-3-2020/

MARGARET BRENNAN: Joining us now is Daniel O'Day, chairman and CEO of Gilead Sciences, that's the pharmaceutical company that makes remdesivir. Good morning to you.

GILEAD CEO DANIEL O'DAY: Good morning, MARGARET. Thank you for having me on.

MARGARET BRENNAN: So this drug shaves about four days off the recovery time of someone hospitalized with coronavirus, according to the government study. Now that your company has this emergency use authorization, how quickly will the drug get to those people who need it?

O'DAY: Well, you know, I think I speak on behalf of all of us at Gilead that we are grateful and really humbled that everything has moved so quickly. You know, it's only been three months since the first case was diagnosed in the United States to the emergency use authorization that was provided this past Friday. That's thanks to a lot of patients and caregivers that participated in our clinical trials. And we are now firmly focused on getting this medicine to the- the most urgent patients around the country here in the United States. And, MARGARET, we intend to get that to patients in the early part of this next week, beginning to work with the government, which will determine which cities are most vulnerable and- and where the patients are that need this medicine.

MARGARET BRENNAN: I think that's important. You're saying you've- you've donated some of this drug to the federal government, and you will work with the federal government to decide where the drug goes? Or is that up to the federal government to decide?

O'DAY: Right, MARGARET. So we've donated the entire supply that we have within our supply chain. And we did that because we acknowledge and recognize the human suffering, the human need here and want to make sure that nothing gets in the way of this getting to patients. And what we will do is- is provide that donation to the U.S. government and they will determine, based upon things like ICU beds, where the course of the epidemic is in the United States. They will begin shipping tens of thousands of treatment courses out early this week and be adjusting that as the epidemic shifts and evolves in different parts, in different cities here in the United States.

MARGARET BRENNAN: Okay- okay, well, we have more to talk about with you, but I have to take a quick break here. So stay with us, and stay with us, all of you as well, please. More with Daniel O'Day in a moment

(COMMERCIAL BREAK)

MARGARET BRENNAN: I want to pick up on this, you said the- the supply of one and a half million doses of remdesivir has been donated to the government. That's enough for what, 150,000 patients or so?

O'DAY: Right, MARGARET. Just to be clear, what we've done is we've donated the entirety of our supply, which is around 1.5 million vials, and that turns into around 100,000 to 200,000 treatment courses depending on whether it's a five-day or a 10-day. And this donation will be made available to patients here in America and the United States and across the world as other regulatory decisions are taken for those countries.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

MARGARET BRENNAN: This drug is clearly going to be in demand since it's the- the first sort of promising development we've had. You were at the White House, has the Trump administration talked to you at all about using the Defense Production Act to somehow mandate that you prioritize the U.S. market over foreign markets?

O'DAY: Yeah, let me say something on the supply and the demand, because, you know, I'm so proud to work with the scientists at Gilead that, you know, that quickly moved and mobilized themselves in January, long before we knew whether the medicine would be available, to increase the supply. This is a long supply process. It used to take around 12 months, and now it takes around six months. And because of the steps we took in January, we'll have significantly more supply in the second half of this year to serve the suffering and the human needs out there. We've been working very closely with the U.S. government and with other governments around the world. In terms of the allocation question, I think we're aligned with the US government to both serve the patients here in the United States and then to be able to also make sure, as a global company based here in the United States, that we can serve other countries around the world as well. We've had very good dialogues with the government and that's going well.

MARGARET BRENNAN: So they haven't talked to you about mandating the U.S. market be prioritized or taking it for the stockpile for example. You can still export it?

O'DAY: That's correct. We have been exporting for clinical trials and for compassionate use, thousands of treatment courses. An- and our collaboration with the government has been such that we've been very transparent with them here in the United States. And we have a good relationship on- on future allocation.

MARGARET BRENNAN: This drug you have to get through an I.V. right now, so it works for hospitalized patients. Will you develop other mechanisms? Does this ever become a pill someone can take at home?

O'DAY: Yes. It's important to note that this medicine is really right now for the most severe patients in the hospital, and it's given by I.V. either through a five-day treatment course or a 10-day treatment course, depending on the stage and nature of the patient. But our scientists have been working since earlier this year to say, are there other ways that we could deliver this medicine, potentially as Dr. Gottlieb mentioned, to earlier patients. And in order to do that, we're looking at formulations such as subcutaneous formulations that may be given outside the hospital setting and possibly an inhaled version. This medicine is not suitable for oral administration because of the way it's metabolized. But there are ways we can look at formulations potentially that would get us to earlier patients and patients outside the hospital setting. That research is still ongoing yet, hasn't yet read out. And we'll certainly keep you up to speed on that.

MARGARET BRENNAN: All right. We will be watching. Thank you very much, Mr. O'Day.

O'DAY: Thank you.

- **450)** 2020-05-05 Siegel E: This is how physics, not math, finally resolved Zeno's famous paradox. Forbes https://www.forbes.com/sites/startswithabang/2020/05/05/this-is-how-physics-not-math-finally-resolves-zenos-famous-paradox/?sh=24f6f51c33f8
- **451)** 2020-05-05 2020-09-18: *Historic St. Mary's Mission & Museum est. 1841*: Fr. Pierre Jean De Smet, S.J., 1801-1873. https://www.saintmarysmission.org/fr-desmet

The Early Montana Missions

Competition for land and resources spurred the Salish to seek what they believed to be the mysterious power of the white man's religion; to gain strength and power over their enemies, the Blackfeet. In the 1830's, the Flathead, Nez Perce and Iroquois tribes sent four delegations to St. Louis in search of Catholic priests, or "Blackrobes". In 1839, they asked Jesuit priest Pierre-Jean De Smet, who three years later followed them back along an ancient trail to the Bitterroot Valley of Western Montana.

The "Blackrobes" established St. Mary's Mission near present-day Stevensville. They taught the native people a belief in Christianity in addition to farming and domestic skills. It was at St. Mary's Mission that Montana's first sawmill was constructed, the first crops were cultivated, and a water-powered gristmill was first put to use.

St. Mary's closed in 1850, and the Jesuit influence expanded with the development of the St. Ignatius Mission. Father De Smet and Father Adrian Hoecken and Joseph Menetrey built several log buildings, including a chapel, two houses, a carpenter's shop and a blacksmith shop. At St. Ignatius, the priority was to establish a mission school to fulfill an educational provision in the Hellgate Treaty of 1855. —On the wall of the one room chapel of the U.S. Department of Agriculture Museum, Missoula, MT.

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- **458)** 2020-05-12 Kesici S, Yavuz S, Bayrakci: Letter: Get rid of the bad first: Therapeutic plasma exchange with convalescent plasma for severe COVID-19. PNAS June 9, 2020; 117 (23) 12526 12527. https://www.pnas.org/content/pnas/117/23/12526.full.pdf
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 - a. But immunization in the 1770s was not what it's like today with a single injection and a low risk of mild symptoms. Edward Jenner didn't even develop his revolutionary cowpox-based vaccine for smallpox until 1796. The best inoculation technique at Washington's disposal during the Revolutionary War was a nasty and sometimes fatal method called "variolation."
 - b. "An inoculation doctor would cut an incision in the flesh of the person being inoculated and implant a thread laced with live pustular matter into the wound," explains Fenn. "The hope and intent was for the person to come down with smallpox.

- When smallpox was conveyed in that fashion, it was usually a milder case than it was when it was contracted in the natural way."
- c. Variolization still had a case fatality rate of 5 to 10 percent. And even if all went well, inoculated patients still needed a month to recover. The procedure was not only risky for the individual patient, but for the surrounding population. An inoculee with a mild case might feel well enough to walk around town, infecting countless others with potentially more serious infections.
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 Published as a commentary in VoxSanguinis (2021) 116, 13-14.

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...The curative effect of convalescent plasma is closely related to the quality, dose, antibody titer and infusion time of the plasma. ...

476) 2020-05-30 Alsuliman T, Alasadi L, Alkharat B, Srour M, Alrstom A: A review of potential treatments to date in COVID-19 patients according to the stage of the disease. Current Research in Translational Medicine 68 (2020) 93 – 104. https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC7260520&blobtype=pdf

Convalescent plasma The FDA has recently approved convalescent plasma for serious or immediately life-threatening COVID-19 infections under emergency Investigational New Drug Application (eINDs) [80]. Convalescent plasma has been previously studied during other epidemics including H1N1 influenza virus pandemic, SARS-CoV-1 epidemic, and the MERS-CoV epidemic. Recently, a preliminary case series of five intubated COVID-19 patients with ARDS showed promising results. These patients received 400 ml of convalescent plasma containing neutralizing SARS-CoV-2–specific antibody (IgG) from recovered COVID-19 donors. All patients had gradual clinical and radiological improvement within 3 days and four patients no longer required respiratory support by day 9, viral loads also became negative within 12 days after transfusion. Seven clinical trials are currently registered [7,38,81].

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To develop therapeutics to treat the 2019 novel coronavirus, the US Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR) will expand an existing collaboration with US biotech Regeneron Pharmaceuticals (Nasdaq: REGN), whose shares rose 4.5% to \$372.16 on the news yesterday.

"Emerging infectious diseases can present serious threats to our nation's health security," said Rick Bright, deputy assistant secretary for preparedness and response and director of the Biomedical Advanced Research and Development Authority (BARDA) at ASPR, adding: "Working as public-private partners like we have with Regeneron since 2014, we can move rapidly to respond to new global health threats."

"The life-saving results seen with our investigational Ebola therapy last year underscore the potential impact of Regeneron's rapid response platform for addressing emerging outbreaks," said Dr George Yancopoulos, president and chief scientific officer of Regeneron. "Our unique suite of technologies expedites and improves the drug discovery and development process at every

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stage, positioning Regeneron to respond quickly and effectively to new pathogens. We are eager to expand our productive collaboration with BARDA and are already working hard to address the novel coronavirus that is causing worldwide concern," he noted.

The BARDA and Regeneron now will leverage their partnership agreement to develop multiple monoclonal antibodies that, individually or in combination, could be used to treat this emerging coronavirus, also known as 2019-nCoV.

Will leverage Regeneron's VelocImmune platform

Medicines developed for 2019-nCoV through the expanded BARDA-Regeneron partnership will leverage Regeneron's monoclonal antibody discovery platform called VelocImmune, part of the company's VelociSuite technology.

In addition to expanded collaboration with Regeneron, BARDA is working with counterparts across the government, including within HHS and with the Department of Defense. The team is reviewing potential vaccines, treatments and diagnostics from across the public and private sectors, particularly products in development for MERS or Severe Acute Respiratory Syndrome (SARS), to identify promising candidates for development to detect, protect against or treat 2019 nCoV.

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<u>Statement 8</u> Convalescent plasma therapy should probably be used for severe and critically ill patients with COVID-19 (Grade 2+, weak recommendation).

<u>Rationle</u> Convalescent plasma has been testified to suppress viremia, shorten the hospital stay, and reduce mortality during several virus epidemics. ...

...regardless of these limitations, since there are still no specific etiological treatments for COVID-19, and convalescent plasma is available, it is reasonable to use it in the treatment of COVID-19 patients.

486) 2020-06-08 Abbasi J: Anthony Fauci, MD, on COVID-19, Schools, and Larry Kramer. JAMA.com. JAMA 2020;324(3): 220-222

https://jamanetwork.com/journals/jama/fullarticle/2767208

Dr. FAUCI: Right now we have a major push on a program to develop monoclonal antibodies, convalescent plasma, and hyperimmune globulin, all of which are founded on the same principle of using an antibody that is directed against the virus for either prophylaxis or treatment. And I think you're going to see it's going to be both. We'd like to have available for those who are at risk—elderly and those with underlying conditions—either monoclonal antibodies or convalescent plasma. That's a very, very high priority.

•

Dr Bauchner: Your equanimity, does it come from your parents? Does it come from your Jesuit education? It's extraordinary under the face of remarkable criticism, almost always unfair.

Dr Fauci:I think it does come a lot from my parents. My father was very much of a tolerant person who would accept people for what they are and very rarely ever criticized anybody. I went to a Jesuit high school in Manhattan, and from there I went to a Jesuit college. I think it was just right for me because I had always been interested in public service and not being somebody that ever attacks anybody, that accepts them for who they are and what they are. So it was kind of the perfect atmosphere to me to be educated in, and I just carried it along with me.

Feuerherd P: Dr. Fauci is dedicated to public service, formed at Jesuit high school. Catholic Review—Inspiring the Archdiocese of Baltimore. 2020 March 30. https://catholicreview.org/dr-fauci-is-dedicated-to-public-service-formed-at-jesuit-high-school/

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Convalescent plasma

Convalescent plasma is also a potentially promising strategy to treat COVID-19. In a recent case study, the clinical status of all the five critically ill COVID-19 patients receiving convalescent plasma showed a significant improvement within 1 week following the infusion, normalization of body temperature, as well as scores of the sequential organ failure assessment. Moreover, within 1-12 days following the infusion, the neutralizing antibody titers of the patients improved and the respiratory samples tested negative fokr SARS-CoV-2 (ref. 62). In another study of 10 severe cases, the viral titers were undetectable following the infusion in seven patients who had previously high viremia⁶³. Previous studies on other respiratory viral diseases provided some evidences on the efficacy of convalescent plasma on treating severe and critical viral diseases. Several studies in SARS patients reported that the use of convalescent plasma was linked to reduced hospital stay and reduced mortality^{64,65}. Clinical trials also showed that in patients with severe H1N1 influenza A, in the 2009 pandemic, therapy with convalescent plasma from patients who recovered, especially within 5 days of symptom onset, resulted in a lower viral load and lower mortality 66,67. Subsequent analysis showed that the mortality of patients with severe acute viral respiratory infections was reduced after therapy with convalescent plasma, while absence of adverse events or complications were observed⁶⁸.

Nevertheless, there are still issues we need to tackle. The first question is when to collect plasma from recovered COVID-19 patients. Recent work by To et al. 25 showed that, day 10 after symptom onset, both IgG and IgM antibodies increased in the majority of patients, while seroconversion was observed with the first 3 weeks. Importantly, the anti-SARS-CoV-2 IgG and IgM antibody levels against the internal nucleoprotein and the spike S1 domain correlated with neutralizing activity. Therefore, it would be ideally to collect convalescent plasma from week 3 after symptom onset. Despite hundreds of patients had recovered from COVID-19, eligible convalescent plasma is quite limited as the donors have to pass physical and laboratory examination, and plasma should be tested for SARS-CoV-2 nuclear acid, HIV-1, HBV, and HCV, as well as antibody titers, to list a few. The second question is deciding which patients and when should receive the convalescent plasma. The effects of convalescent plasma are difficult to observed when used in critical patients with multiple organ failure, as the viral load in this kind of population is quite high. Hence it is preferably to use convalescent plasma in mild patients whose diseases was deteriorating in their early phase of diseases. Normally, in COVID-19, the viral load peaked at the first week of illness, and then slowly decline during the subsequent seek²⁵. Accordingly, in principle, the most effective to administer the convalescent plasma is at the early phases of the disease. The biggest challenge is that it is quite difficult to identify which patient will deteriorate in the early stage. Several risk factors including older age, male, multiple comorbidities, elevated IL-6, and elevation in D-dimer levels that are associated with bad outcomes may be used as surrogate markers¹⁰. Provided further studies demonstrate its efficacy in appropriately selected patients, the next step would be the production of humanized antibody at biotechnological level.

2020-06-10 Yigenoglu TN, Hacibekiroglu T, Berber I, Dal MS, Basturk A, Namdaroglu S, Korkmaz S, Ulas T, Dal T, Erkurt MA, Turgut B, Altuntas F: CONCISE REVIEW Convalescent plasma therapy in patients with COVID-19. J Clin Apher 2020; 35: 367-373. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jca.21806

490) **2020-06-10** Harris KM: Letter at the request of Dr. Fauci designating NIAID Case# 12276. 06 Appendices A-H copy; Appendix G—NIH and FDA responses including the establishment NIAID #12276 6-10-2020; NIH and FDA responses including 6-6-

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While the website above the generalities, to submit FOIA request is somewhat complicated and the following disclaimer for the NIH—National Institutes of Health in part is: ...Please submit all requests through our online portal (link below) rather than mail, fax, or courier, to ensure timely logging of your requests....

First (1): https://www.nih.gov/institutes-nih/nih-office-director/office-communicationspublic-liaison/freedom-information-act-office/submitting-foia-requests

Next (2): click on the Submit a FOIA Request:

Next (3): The following disclaimer will show up which after reading it, if one wishes to proceed, you should click on "I Accept":

Submit a FOIA Request

2020-06-11: Stankiewicz K: Regeneron sees 'a lot of reason for hope' as human testing of its coronavirus drug begins. CNBC. https://www.cnbc.com/2020/06/11/regeneronbegins-human-testing-of-its-coronavirus-antibody-drug.html

KEY POINTS

- Regeneron Pharmaceuticals announced Thursday that it's started the first clinical trial of its experimental coronavirus antibody drug.
- The antibody cocktail is being tested in four human populations, with two groups of people receiving the drug as a treatment and two as a possible prevention.
- "I think there's a lot of reason for hope," Regeneron's chief scientific officer, Dr. George Yancopoulos, said on CNBC's "Squawk Box."
 - Regeneron Pharmaceuticals announced Thursday that it's started the first clinical trial of its experimental coronavirus antibody drug.
 - The antibody cocktail is being tested in four human populations. Two groups of people will receive the drug to test its effectiveness as a treatment for Covid-19; the other two will receive it as a possible prevention.
 - "We'll be hopefully to quickly test the safety and then start understanding the efficacy for four major different settings of this virus challenge," Regeneron's chief scientific officer, Dr. George Yancopoulos, said on CNBC's "Squawk Box."

-- May 30, 2022 -----

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- Yancopoulos said he thinks that, "if all goes well," the company could have "definitive data" within a few months on the effectiveness of the antibody cocktail.
- "I think there's a lot of reason for hope," Yancopoulos said, noting the company's work on Ebola. But he also stressed the unpredictable nature of science and biology, saying "there's always reasons to be concerned and to be cautious."
- "So we're going to be moving forward very carefully, hand-in-hand in with the FDA, and we hope sooner rather than later we can get answers that can really make a difference," he said.
- Regeneron is the latest company to begin trials for a potential Covid-19 therapy. Eli Lilly, which began trials of its antibody drug <u>earlier this month</u>, said a treatment could be authorized, <u>if all goes well</u>, for use as early as September. In scientific trials so far, <u>Gilead Sciences</u>'s antiviral remdesivir is the only drug to <u>show some effectiveness</u> in treating the disease.
- There are more than 7.4 million confirmed cases of Covid-19 in the world, including over 2 million in the U.S., according to the latest <u>data from Johns Hopkins University</u>. More than 417,100 people have died worldwide, with over a quarter of the fatalities in the U.S.
- Regeneron's drug is being tested on four distinct types of patients, including "the sickest patients" who are hospitalized and on a ventilator or oxygen support, Yancopoulos said. It's also being tested to see whether it can prevent high-risk people from contracting the disease, such as health-care workers.
- The drug, known as REGN-COV2, is a combination of two antibodies. Yancopoulos said Regeneron firmly believes this is the correct approach to treat Covid-19 when using antibodies.
- "Just like with conventional, old fashion antiviral drugs, giving one can have
 enormous benefit initially but it can lead to the selection and the arise of escaped
 viral mutants, which can could be very dangerous and risky," he said. "What we
 showed is that in order to prevent this, you have to give these antibodies in
 cocktails."
- 492) 2020-06-15 Marovich M, Mascola JR, Cohen MS: Monoclonal antibodies for prevention and treatment of COVID-19. JAMA 2020 June 15; 324: 131-132. https://jamanetwork.com/journals/jama/fullarticle/2767383

The coronavirus disease 2019 (COVID-19) pandemic has created a worldwide crisis and inspired an urgent search for prevention and treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Attention has focused on the development of vaccines, new antiviral agents, and convalescent plasma infusions. Monoclonal antibodies have received less attention even though neutralizing antibodies are a key component of protective immunity for most viral diseases. Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential for both therapeutic and prophylactic applications, and can help to guide vaccine design and development. 1

Conclusions

Neutralizing antibodies have an important role in the protection or recovery from many viral infections. Several monoclonal antibody products will enter clinical trials over the next few months and be assessed for their ability to limit or modify SARS-CoV-2 infection. In addition, a drug that reliably prevented progression of COVID-19 would greatly reduce the concerns and uncertainty associated with SARS-CoV-2 infection and give physicians a therapeutic tool they

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must have for their patients. Establishing the therapeutic or prophylactic efficacy of monoclonal antibodies would be a major advance in the control of the COVID-19 pandemic.

- **493)** 2020-06-15 FDA: Coronavirus (COVID-19) Update: FDA revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and
- 494) 2020-06-18 Mahant V: "Right-to-Try" experimental drugs: an overview. J Transl Med 2020; 18: 253-263. NCBI published version: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7309195/ Pdf published version: https://translational-medicine.biomedcentral.com/track/pdf/10.1186/s12967-020-02427-4.pdf

In May 2018, President Donald Trump signed the "Right-to-Try" Act [5]. The legislation overcame many of the regulatory barriers, limited the risks to the sponsor while implementation of the act inherently burdened the sponsor. The "Right-to-Try" legislation is in essence a derivative of the Expanded Access Programs (EAPs). Advocates such as patients, families, friends and advocacy groups of the "Right-to-Try" legislation argue that the legislation is in line within the pre-existing framework of EAPs and that the legislation: (i) provides a "streamlined" avenue for making eligible drugs available to eligible patients with no other options; (ii) it increases patient's engagement; (iii) it is a patient's journey of self-actualization; (iv) it empowers the patient about his or her own health, well-being and quality of life; (v) it provides optimism and access to novel interventions with potential therapeutic benefits that may prolong life and improve quality of life; and (vi) the patient can be treated in the USA with valuable family time, more comfort and fewer risks than being treated overseas. The critics, on the other hand, argue: (i) there is an inherent safety risk that may potentially cause more harm to the patient or even death than the benefit because the experimental drug did not undergo rigorous testing; (ii) there is a lack of oversight by the FDA, except posting of the consolidated annual summary report; (iii) the patient in most cases has limited understanding of the informed consent due to complexity and confusion of the medical terminology used in the consent form; (iv) there are therapeutic misconceptions combined with high expectations and optimism by the patient; (v) there is potentially a considerable financial burden by the patient or the patient's family because payors currently do not provide coverage and deny hospice care; (vi) there is a potential loss of trust in the regulatory agency, the sponsor and the health care provider; and (vii) there is a liability "immunity" for the health-care provider, including the drug sponsor for potential negative outcomes of the treatment unless the medical provider and the sponsor were engaged in "gross negligence, reckless or "wilful misconduct." ...

The implications of ethics, law, regulations, government policies, constitutional rights by terminal ill patients, patient advocacy groups, including stakeholders about the pros and cons echoed through the "ecosystem" of early access to investigational drugs. Under the "Right-to-Try" legislation, the eligibility to participate include: (i) the patient must have been diagnosed with a debilitating or life-threatening disease; (ii) the patient must have failed all standard of care treatments; (iii) the experimental or the investigational drug must have completed at least phase 1 trial; (iv) the patient must have signed an informed consent [6]; and (vi) the pharmaceutical company must be able to provide the experimental drug to the patient. Due to the potentially negative outcome about the therapeutic efficacy combined with the safety issues, most sponsors developing medications for life-threatening diseases have had reservations about participating in expanded access or the "Right-to-Try" programs. To de-risk the potential negative outcomes and the implications combined with an opportunity to target a much larger number of patients than to a few eligible patients under the

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early access programs, the sponsors' primary goal --has been to have full FDA approval of the drug. The drug approval process, of course, is lengthy and highly risky due to potential clinical trial failures along each step of the approval process. It is an expensive process—currently, estimated to be between US\$ 1.9–2.5 billion [7, 8]. ...

Conclusion

The progress made on several fronts in healthcare and the concerted efforts by the stakeholders, including the integral role of agencies such as World Health Organization (WHO) and Global Health Council (GHC) over the last few decades for the treatment of diseases, patient and public engagements, the role of healthcare practitioners, the role of education, data ownership, data sharing, transparency, privacy, ethics, standardization across the multi-industries, regulations, compliance, funding of programs, payment by medical insurance companies, including global policy development and implementation currently present limited opportunities and many challenges for the "Right-to-Try" experimental drugs for the treatment of life-threatening diseases. The "Right-to-Try" experimental drug is nevertheless a major "milestone" along the journey and its full impact on treating life-threatening diseases such as cancer and infectious diseases such as COVID-19 remain to be seen. One of the biggest impacts of emergency use of experimental drugs and compassionate drugs or "repurposing" of drugs is unfolding during the current coronavirus pandemic crisis.

495) 2020-06-19 McEnany K: White House Press Conference, June 19, 2020. https://www.youtube.com/watch?v=GxX6CgI7RJ4

> ...Finally, well second, to finally, we are encouraged that we continue to gather positive data on a number of therapeutics: heparin; dexamethasone or steroids as it's more commonly known; convalescent plasma; and Remdesivir have all shown promise in treating coronavirus. Preliminary findings in a large UK-based recovery trial found that when steroids were used there was a 30% reduction in death for coronavirus patients on ventilators. The FDA is reviewing this recovery trial data now. Additionally, on convalescent plasma there's more encouraging news in partnership with mayo clinic the Trump administration move very quickly on this therapy and it's earliest days recognizing that it showed promise. Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promising--this has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages. The lead investigator of this Mayo Clinic study, Dr. Michael Joyner, summed up his work in saying that convalescent plasma "continues to look promising" noting the "excellent news of this study which covered a diverse population of patients about 20% were African-American, nearly 35% Hispanic, 5% Asian, and 40% women. Prior experience with respiratory viruses and some data that have emerged globally suggest convalescent plasma has the potential to lessen the severity or shorten the length of the illness caused by COVID-19. The results from the Mayo underscore that promise. As you can see, the Trump administration and FDA led on identifying convalescent plasma as a therapeutic and the results are encouraging...

- **496)** 2020-06-20 KPIX 5, CBS SF, BayArea: Photos: Juneteenth Protester Topple Golden Park Statues of Serra, Key, Grant. https://sanfrancisco.cbslocal.com/2020/06/20/juneteenth-protesters-topple-golden-gate-park-statues-of-junipero-serra-francis-scott-key-u-s-grant/
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inflammatory damage in COVID-19. Proceedings of the National Academy of Sciences. https://www.pnas.org/content/117/23/12529

First of all, this study was a pilot trial and the aim was to investigate the safety of CP transfusion, which was defined as the primary endpoint (3). We nevertheless also explored the possible therapeutic benefits of CP by examining its effectiveness in neutralizing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in ameliorating clinical symptoms and paraclinical criteria in recipients. Indeed, the adverse effect was minor, whereas a quickly improved outcome of 10 severe COVID-19 patients was observed. There are of course a number of issues to be addressed, such as the confirmation of the clinical effectiveness in a phase II controlled, randomized trial.

Second, the objective for CP transfusion in severe COVID-19 therapy is based on an in-depth understanding of disease mechanisms. The pathogenesis of this epidemic involves the interaction between viral replication of SARS-CoV-2 and human immune response (4). Particularly, in severe or critical COVID-19 cases, lung alveolar macrophages or epithelial cells could produce various proinflammatory cytokines and chemokines, which recruit monocytes and neutrophils to the infection site to clear the virus particles and infected cells, resulting in uncontrolled inflammation. The uncontrolled virus infection leads to more macrophage infiltration and a further worsening of lung injury. Therefore, the key point of CP therapy is to neutralize the virus and to interrupt the vicious cycle of excessive activation of the immune response in severe patients. In our study, 200 mL CP containing neutralized antibody above 1:640 rapidly cleared the viremia and achieved clinical improvement. Considering the accessibility of plasma donors, using CP as replacement fluid for the therapeutic plasma exchange may be not feasible.

Third, the optimal treatment time and dose of CP need to be determined by the knowledge on viral proliferative kinetics. Zhou et al. (5) reported that the median viral shedding time was 20.0 d in survival patients. Huang et al. (6) observed that the viral load gradually decreased in the respiratory tract after 7 d of illness onset but can be detected after 28 d of illness onset in two-thirds of critically ill patients. Chen et al. (7) found the serum viremia was detected in 29.4% (5/17) critically ill patients and was significantly correlated with the level of interleukin-6. Thus, monitoring the dynamic changes of interleukin-6 level, which was significantly elevated in COVID-19, may help to determine the optimal treatment time, generally within 2 wk.

Finally, the optimal time for collecting CP should be determined by the time and level of total antibody production in convalescent patients. The presence of antibodies was <40% among patients within 1 wk since onset and rapidly increased to 100.0% (antibody), 94.3% (immunoglobulin M), and 79.8% (immunoglobulin G [IgG]) since day 15 after onset (8). Also, the neutralizing antibody titer was correlated with the IgG antibodies (9). The median duration of hospitalization for COVID-19 patients was 12.0 d ($\underline{10}$). In our study, all of the donors were recovered from the common type of COVID-19. Therefore, the collection of CP from the convalescent patients may be 3 wk after the illness onset, and routine inactivation of plasma should be performed for elimination of potential existing virus. The optimal dose of CP can be calculated based on an empirical formula: volume (liters) = weight of the recipient (kilograms) × the antibody titer of CP

498) 2020-06-22 Hurd D, Smith C, Quintana S: Demonstrators topple statues in San Francisco's Golden Gate Park. NBC BAY AREA.

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very important article on the pathophysioiology of the inflammatory storm which is relatively (>8 days) late component of COVID-19 pathologic symptomatology versus the earlier viremic phase (0 to \sim 8 days).

Abstract

Neither the disease mechanism nor treatments for COVID-19 are currently known. Here, we present a novel molecular mechanism for COVID-19 that provides therapeutic intervention points that can be addressed with existing FDA-approved pharmaceuticals. The entry point for the virus is ACE2, which is a component of the counteracting hypotensive axis of RAS. Bradykinin is a potent part of the vasopressor system that induces hypotension and vasodilation and is degraded by ACE and enhanced by the angiotensin1-9 produced by ACE2. Here, we perform a new analysis on gene expression data from cells in bronchoalveolar lavage fluid (BALF) from COVID-19 patients that were used to sequence the virus. Comparison with BALF from controls identifies a critical imbalance in RAS represented by decreased expression of ACE in combination with increases in ACE2, renin, angiotensin, key RAS receptors, kinogen and many kallikrein enzymes that activate it, and both bradykinin receptors. This very atypical pattern of the RAS is predicted to elevate bradykinin levels in multiple tissues and systems that will likely cause increases in vascular dilation, vascular permeability and hypotension. These bradykinin-driven outcomes explain many of the symptoms being observed in COVID-19.

eLife digest

In late 2019, a new virus named SARS-CoV-2, which causes a disease in humans called COVID-19, emerged in China and quickly spread around the world. Many individuals infected with the virus develop only mild, symptoms including a cough, high temperature and loss of sense of smell; while others may develop no symptoms at all. However, some individuals develop much more severe, life-threatening symptoms affecting the lungs and other parts of the body including the heart and brain.

SARS-CoV-2 uses a human enzyme called ACE2 like a 'Trojan Horse' to sneak into the cells of its host. ACE2 lowers blood pressure in the human body and works against another enzyme known as ACE (which has the opposite effect). Therefore, the body has to balance the levels of ACE and ACE2 to maintain a normal blood pressure. It remains unclear whether SARS-CoV-2 affects how ACE2 and ACE work.

When COVID-19 first emerged, a team of researchers in China studied fluid and cells collected from the lungs of patients to help them identify the SARS-CoV-2 virus. Here, Garvin et al. analyzed the data collected in the previous work to investigate whether changes in how the body regulates blood pressure may contribute to the life-threatening symptoms of COVID-19.

The analyses found that SARS-CoV-2 caused the levels of ACE in the lung cells to decrease, while the levels of ACE2 increased. This in turn increased the levels of a molecule known as bradykinin in the cells (referred to as a 'Bradykinin Storm'). Previous studies have shown that bradykinin induces pain and causes blood vessels to expand and become leaky which will lead to swelling and inflammation of the surrounding tissue. In addition, the analyses found that production of a substance called hyaluronic acid was increased and the enzymes that could degrade it greatly decreased. Hyaluronic acid can absorb more than 1,000 times its own weight in water to form a hydrogel. The Bradykinin-Storm-induced leakage of fluid into the lungs combined with the excess hyaluronic acid would likely result in a Jello-like substance that is preventing oxygen uptake and carbon dioxide release in the lungs of severely affected COVID-19 patients.

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Therefore, the findings of Garvin et al. suggest that the Bradykinin Storm may be responsible for the more severe symptoms of COVID-19.

Further experiments identified several existing medicinal drugs that have the potential to be repurposed to treat the Bradykinin Storm. A possible next step would be to carry out clinical trials to assess how effective these drugs are in treating patients with COVID-19. In addition, understanding how SARS-Cov-2 affects the body will help researchers and clinicians identify individuals who are most at risk of developing life-threatening symptoms.

Introduction

The COVID-19 beta-coronavirus epidemic that originated in Wuhan, China in December of 2019 is now a global pandemic and is having devastating societal and economic impacts. The increasing frequency of the emergence of zoonotic viruses such as Ebola, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) (among others) are of grave concern because of their high mortality rate (10%–90%). Fortunately, successful containment of those pathogens prevented global-scale deaths. In contrast, the current estimates of mortality for COVID-19 are much lower (~4%), but the virus has now infected more than nine million people and caused nearly a half a million deaths. The cause of mortality appears to be heterogeneous and although it typically targets older individuals, younger individuals are also at risk. A key to combating the pandemic is to understand the molecular basis of COVID-19 that may lead to effective treatments.

Paradoxically, an opportunity that was unavailable with SARS, MERS or Ebola has arisen because of the intense, globally distributed focus of medical and scientific professionals on COVID-19 that is providing a wealth of highly diverse information and data types. Nine bronchoalveolar lavage (BAL) samples were originally collected from patients in Wuhan China for RNA sequencing in order to determine the etiological agent for COVID-19 and resulted in the sequence of the first SARS-CoV-2 viral genome. However, the human reads from these samples were discarded 3. Here, we analyze the human RNA-seq data from these BAL samples alongside 40 controls.

Results and Discussion

The Renin Angiotensin System (RAS)

Although pre-existing hypertension is a reported comorbidity for COVID-19, recent reports indicate hypotension is highly associated with COVID-19 patients once in the hospital (Rentsch, 2020). The RAS is an important pathway linked to these conditions because it maintains a balance of fluid volume and pressure using several cleavage products of the peptide angiotensin (AGT) and their receptors (Arendse et al., 2019, Flores-Muñoz et al., 2011, Carey, 2017). The most well-studied peptide is angiotensin II (Ang II), which typically generates vasoconstriction and sodium retention via the AGTR1 receptor and vasodilation and natriuresis when binding to the AGTR2 receptor. The RAS also includes several other lesser known peptides that are highly important; Ang1-7 binds to the MAS1 receptor, generating anti-inflammatory and vasodilatory effects, and Ang1-9 binds to the AGTR2 receptor. Ang II is produced by the enzyme ACE whereas Ang1-7 is generated by the combination of ACE and ACE2 activity and Ang1-9 by ACE2 alone. It is important, therefore, to consider all of these components in the context of the others and not any one in isolation.

ACE2 is also the main receptor for the SARS-CoV-2 virus and is not highly expressed in normal lung tissue based on the Genotype-Tissue Expression (GTEx, gtexportal.org) six population.

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However, results from our differential gene expression analysis of RAS genes in cells taken from BAL samples from individuals presenting with severe symptoms of COVID-19 (Zhou et al., 2020) demonstrates upregulation of ACE2 (199 fold) and disruption of this system compared to controls. In the COVID-19 samples, AGT (34 fold) and the enzyme that activates it (REN, 380 fold) are increased compared to controls whereas the enzymes that produce most of the cleavage products, including ACE (-8 fold), are downregulated, which will likely result in a shift of the entire RAS to produce Ang1-9. In addition, the AGTR1 (430 fold) and AGTR2 (177 fold) receptors are upregulated in BAL COVID-19 samples.

Given the central role that the angiotensin and bradykinin (BK) peptides play in COVID-19 based on our gene expression analysis from BAL samples, we next focused on the RAS- and BK-related gene pathways in lung tissue from the GTEx population; specifically, the networks of genes that are correlated and ani-correlated with the expression of the angiotensin receptors AGTR2 and AGTR1. This subset of genes was annotated with functional information and cell type involvement which resulted in a network (Figure 1) that, as would be expected, demonstrates their extensive involvement in arterial and vascular resistance and blood flow via microvascular dilation, flow, and fluid balance. The genes on the left side of the network are extensively involved in vasoconstriction and contain, among others, ACE, AGTR1, BDKR2, Nitric Oxide Synthase-1, and -2 (NOS1 and NOS2). The right side of the network is extensively involved in decreased arteriolar resistance (vasodilation), increased vascular permeabilization, and altered fluid balance and includes, among other genes, ACE2, AGTR2, and the Vitamin D Receptor (VDR). Surprisingly, we find that both sides of the network are also clearly involved in immune system modulation.

Figure 1

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Functionally annotated network of genes involved in the hypertension-hypotension axis whose expression across the GTEx population is correlated and anticorrelated with the AGTR1 and AGTR2 receptors.

When ACE is downregulated and ACE2 and the BK pathway is upregulated in the lungs of COVID-19 patients it leads to the hypotension, vascular permeability, and the Bradykinin Storm that explains much ... see more

The bradykinin system

Although not as widely discussed as angiotensin, BK is another potent regulator of blood pressure and can be considered essentially an extension of the RAS (Schmaier, 2002). Briefly, similar to the angiotensin peptides, BK is produced from an inactive pre-protein kininogen (either circulating - HMWK or tissue - LWMK) through activation by the serine protease kallikrein (Figure 2A). Kallikrein is represented by a cluster of serine proteases (KLK1-KLK15) on chromosome 19 with different tissue distributions; KLKB1 (on chromosome 4) is normally expressed in the pancreas and is responsible for circulating (plasma) kallikrein. These proteases are inactivated by zinc and several are known co-receptors for viruses including influenza (Kalinska et al., 2016). KLKB1 is activated by FXII of the intrinsic coagulation pathway, which is normally kept in check by the C1-Inhibitor encoded by SERPING1 (Figure 2A). This has the vital ancillary effect of inhibiting the feedback loop of FXII activation by kallikrein (Kaplan and Ghebrehiwet, 2010).

Figure 2

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Critically disrupted RAS and Bradykinin pathways in COVID-19 BAL samples.

(A) Significantly differentially expressed genes: red ovals indicate genes upregulated in COVID-19, blue are downregulated, colors are scaled to the log2-fold-change values for COVID-19. The overall ... see more

Similar to AGTR2 stimulation, BK induces vasodilation, natriuresis, and hypotension upon activation of the BDKRB2 receptor. BK is tightly integrated with the RAS as BK receptor signaling is augmented by Ang1-9, likely by resensitization of the BDKRB2 receptor (Chen et al., 2005; Marcic et al., 1999; Erdös et al., 2002) and also because ACE degrades and inactivates BK. Interestingly, ACE has a higher affinity for BK than it does for AGT (Cyr et al., 2001) and therefore under conditions where ACE is low, the vasopressor system is tilted toward a BKdirected hypotensive axis (Figure 2A). In addition to its role in pressure and fluid homeostasis, BK is a normal part of the inflammatory response after injury and acts to induce pain via stimulation of the BDKRB1 receptor by BK1-8 (Jacox et al., 2014), which also causes neutrophil recruitment and increases in vascular permeability (Stuardo et al., 2004; Araújo et al., 2001; Hofman et al., 2016; Figure 2B). BK1-8 is produced by the enzyme carboxypeptidase N (CPN1 671 fold) acting on BK.

As with the RAS, the BK system is also severely affected in the COVID-19 BAL samples. The expression of the BK precursor kiningeen and nearly all of the kallikreins are undetected in controls but expressed in COVID-19 BAL (Figure 2A). Most of the enzymes that degrade BK, including ACE, are downregulated (-8 fold) in COVID-19 BAL compared to controls, directing BK1-9 and BK1-8 to the upregulated receptors BKB2R (207 fold) and BKB1R (2945 fold), respectively. Of note, the pain-receptor BKB1R is normally tightly controlled and expressed only at very low levels in nearly all tissues in GTEx, but in the case of COVID-19 BAL, both BK receptors are expressed whereas they are virtually undetected in controls. Finally, F12 is unchanged but the SERPING1 (-33 fold) gene that encodes the C1-Inhibitor that inhibits FXII is highly down-regulated, which would result in even further increases in BK in COVID-19 patients given its role in KLKB1 activation (Schmaier, 2016). As described below, the resulting Bradykinin Storm is likely responsible for most of the observed COVID-19 symptoms.

Hyaluronic Acid synthesis and degradation

Hyaluronic acid (HA) is a polysaccharide found in most connective tissues. HA can trap roughly 1000 times its weight in water (Cowman and Matsuoka, 2005) and when bound to water the resulting hydrogel obtains a stiff viscous quality similar to 'Jello' (Necas et al., 2008). HAS1, HAS2 and HAS3 are genes that encode hyaluronan synthases which are integral membrane proteins responsible for HA production (Necas et al., 2008). HA is degraded by hyaluronidases encoded by HYAL1 and HYAL2. Proteins encoded by other genes in this family (HYAL3 and HYAL4) do not appear to have a hyaluronidase activity (Harada and Takahashi, 2007; Kaneiwa et al., 2010). HYAL1 encodes a lysosomal hyaluronidase (Hyal-1) active at low pH and is responsible for intracellular degradation of HA (Harada and Takahashi, 2007). HYAL2 encodes a membrane-bound hyaluronidase (Hyal-2) responsible for extracellular degradation of HA (Harada and Takahashi, 2007). Both Hyal-1 and Hyal-2 are dependent on CD44 (an HA receptor) for activity (Harada and Takahashi, 2007).

As with the RAS and BK systems, the genes encoding HA synthesis and degradation are also severely affected in the COVID-19 BAL samples. There is significant upregulation of the genes involved in HA synthesis: HAS1 (9113 fold), HAS2 (493 fold), and HAS3 (32 fold). The CD44 gene that encodes the HA receptor required for HA degradation and the gene encoding extracellular hyaluronidase HYAL2 are both downregulated (-11 and -5 fold respectively) in the

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BAL fluid of COVID-19 patients. HYAL1 is not expressed in the BAL fluid of controls or the COVID-19 patients. The result of these shifts in expression would be likely to cause an increase in the amount of HA in the bronchoalveolar space of the lungs which, combined with the vascular hyperpermeability caused by BK, could form a viscous hydrogel that would negatively impact gas exchange (Figure 3). In fact, HA in BAL fluid has previously been associated with acute respiratory distress syndrome (ARDS) where there was a significant anticorrelation between the concentration of HA and the pulmonary oxygenation index (Modig and Hällgren, 1989; Hällgren et al., 1989). HA has also been associated with pulmonary thrombosis and/or ground glass opacities in radiological findings (Bhagat et al., 2012; Han et al., 2019; Jang et al., 2014).

Figure 3

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The upregulation of hyaluronan synthases and downregulation of hyaluronidases combined with the BK-induced hyperpermeability of the lung microvasculature leads to the formation of a HA-hydrogel that inhibits gas exchange in the alveoli of COVID-19 patients. Although not the focus of the present study, coagulopathy is commonly reported in cases of COVID- 19 (The Lancet Haematology, 2020), and there are suggestions in the literature of links between RAS and coagulopathy. The Ang1-9 peptide that is increased in COVID-19 BAL stimulates thrombosis by inhibiting fibrinolysis (Mogielnicki et al., 2014). In addition to BK, ACE also degrades the antifibrotic peptide N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), which is produced from thymosin beta-4 (TMSB4X, -130 fold) (Kanasaki, 2020). Increased fibrinolysis could therefore be achieved by increasing ACE, or by administering thymosin beta-4, which is currently in clinical trials for the treatment of cardiovascular disorders (Timbetasin). If TMSB4X is, in fact, protective, it could explain the lower incidence of COVID-19 induced mortality in women (Jin et al., 2020) because it is found on the X chromosome and escapes X-inactivation. Women therefore would have twice the levels of this protein than men, which is supported by our BAL analysis (-207 fold in males, -131 fold in females).

In addition, both the RAS and BK pathways have previously been tied to HA. It was found that Angiotensin II increased CD44 expression and hyaluronidase activity (Bai et al., 2016). As discussed above, COVID-19 likely significantly downregulates the production of Angiotensin II which is consistent with the decrease in CD44 expression that is seen in the BAL fluid of SARS-CoV-2 infected patients. Furthermore, IL2 was recently reported to be highly upregulated in symptomatic but not asymptomatic COVID-19 patients (Long et al., 2020; Paegelow et al., 1995; Mustafa et al., 2002) and is upregulated (21 fold) in the BAL samples compared to controls. This cytokine is induced by BK in the lung, and causes vascular leakage syndrome (VLS), which appears to be mediated through CD44. Interestingly, CD44 knockout mice displayed reduced IL2induced VLS, suggesting this may be a valuable target for COVID-19 intervention.

Clinical description of COVID-19

According to the CDC, the majority of SARS-CoV-2 infections are asymptomatic or mild. Those that proceed to more severe forms present with fever, a non-productive cough that may result in hemoptysis and shortness of breath. Other common symptoms are myalgia, fatigue, sore throat, nausea, vomiting, diarrhea, conjunctivitis, anorexia, and headache (cdc.gov/coronavirus/2019ncov/hcp/clinical-guidance-management-patients.html). Reports from blood studies include leukopenia, eosinopenia, neutrophilia, elevated liver enzymes, C-reactive protein, and ferritin (Fan et al., 2020; Huang et al., 2020; Goyal et al., 2020). Furthermore, autopsies have reported extensive hyaline membrane formation in the lungs of COVID-19 patients (Barton et al., 2020; Xu

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et al., 2020; Adachi et al., 2020; Mong et al., 2020). Specifically, histological analysis of the lungs of a deceased COVID-19 patient showed organizing hyaline membranes in the early stages of alveolar lesions and prominent hyaline membranes in the exudative phase of diffuse alveolar damage (Adachi et al., 2020). In a seperate post mortem study of lung tissue from COVID-19 patients, microscopic examination found 'numerous hyaline membranes without evidence of interstitial organization' (Barton et al., 2020). Furthermore, in another autopsy study of a COVID-19 patient, histological analysis found extensive hyaline membranes, which the authors interpreted as indicative of ARDS (Xu et al., 2020). Finally, a meta-analysis showed that there was a statistically significant 4.6 fold difference in lung weight of COVID-19 patients versus controls, which they conclude is consistent with the HA-hydrogel formation known to occur in ARDS (Mong et al., 2020).

Although much focus has been on the lung due to the need for ventilator support of end-stage disease, COVID-19 also affects the intestine, liver, kidney, heart, brain, and eyes (Wadman, 2020). Nearly one-fifth of hospitalized patients experience cardiac injury (Shi et al., 2020), many of whom have had no history of cardiovascular problems prior to infection. Responses include acute myocardial injury, myocarditis, and arrhythmias (Driggin et al., 2020) that may be due to viral infection directly, which is consistent with high expression of the SARS-CoV-2 receptor ACE2 in cardiac tissue (gtexporta.org). An important extension of the RAS in controlling cardiac contraction and blood pressure is the potent inotrope apelin (APLN), which acts as an NOdependent vasodilator when its receptor (APLNR) heterodimerizes with BDKRB1 (Bai et al., 2014). APLN (98 fold), APLNR (3190 fold) and BDKRB1 (2945 fold) are all upregulated in COVID-19 BAL. As with BK and ANG derived peptides, APLN is inactivated by Neprilysin (MME), which is significantly downregulated in the BAL samples from COVID-19 individuals (-16 fold). Therefore, increased APLN-signaling can be added to the imbalanced RAS.

In addition to cardiac dysfunction, neurological involvement in COVID-19 was revealed after an MRI assessment of COVID-19-positive patients with encephalopathy symptoms in France identified enhancement in leptomeningeal spaces and bilateral frontotemporal hypoperfusion (Helms et al., 2020) which are consistent with increased vascular permeabilization in the brain. Furthermore, earlier reports from China indicate high frequencies of dizziness, headache, as well as taste and smell impairment (Mao et al., 2020). The most recent reports from the United States and China indicate that 30–50% of COVID-19 patients experience adverse gastrointestinal symptoms (Cholankeril, 2020; Pan et al., 2020). Direct infection by the virus and damage to the kidney was also observed, specifically in the proximal tubules (Su et al., 2020). These latter two findings are not surprising given the higher expression of ACE2 in these tissues compared to tissues overall (gtexportal.org), which would facilitate infection by the virus. Finally, COVID-19 patients also frequently display skin rashes including 'covid-toe' that appear to be related to dysfunction of the underlying vasculature.

Bradykinin Storms: A model of SARS-CoV-2, COVID-19, and BK-driven Vascular Permeabilization

Based on previous work in SARS-CoV-1 and SARS-CoV-2, it is likely that this new coronavirus enters host cells in nasal passages where the receptor ACE2 is moderately expressed. Migration to throat tissues and passage through the stomach is then possible given that SARS-CoV-2 can survive the extreme pH of the gastric tissues (Chin et al., 2020) and infection could then expand into the intestines where ACE2 levels are high (GTEx Consortium, 2013). Initial infection might not occur in the lung epithelium given that ACE2 is undetectable or expressed at extremely low levels there (GTEx Consortium, 2013). Following infection, the single polypeptide that is translated from the virus' positive-strand RNA genome is cleaved into active proteins by the nonstructural protein 3CLpro protease. This protein is then repurposed by the virus to inactivate the

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host cells' first line of defense, interferon, most likely by degrading the NFkappaB activating factor IKK-gamma as has been shown to happen in the porcine coronavirus PEDV (Wang et al., 2016).

Aside from self-protection, the suppression of NFkappaB (–9 fold reduced in BAL samples) directly affects the RAS as NFkappaB normally induces the expression of ACE by binding to its promoter and increasing transcription (Garcia et al., 2016; Figure 2A). This likely relates to the role of ACE in the innate immune response that is independent of its actions on the vascular system (Bernstein et al., 2018). The virus therefore acts pharmacologically as an ACE inhibitor by reducing its RNA expression more than 10-fold, which is supported by our BAL RNA-seq analysis. Additionally, ACE2 expression is normally downregulated in-part by Ang II (Patel et al., 2016). As Ang II is the catalytic product of ACE, it would seem that the virus's ability to decrease ACE expression would have the effect of upregulating ACE2 (199 fold in our BAL analysis). In some patients, severe pulmonary involvement could occur when the virus is introduced into the intestinal lymph vessels and moves up the lymphatic system (Chen, 2020), enters the bloodstream at the thoracic duct and moves through the heart and into the lung microvasculature where it could attack cells in the lungs that now express ACE2 due to virus-induced upregulation.

Given that the high levels of ACE in the vascular bed of the lung are the major producer for circulating angiotensin-derived peptides (Studdy et al., 1983), establishment of SARS-CoV-2 in the lung will have profound effects. Downregulation of ACE here (confirmed in BAL samples from COVID-19 patients) will result in the diversion of the RAS to produce the BK-augmenting peptide Ang1-9, exacerbating BK-effects, such as pain sensitization and increased vascular permeability on a system-wide level. Expansion of this imbalance as described above (Figure 2), increases levels of BK and will result in increased vascular permeability in tissues that have been infected by SARS-CoV-2 and be most severe in those that are normally regulated by ACE. ACE may also provide a key diagnostic point as half of the variation amongst individuals can be explained by an insertion/deletion polymorphism of the gene (Rigat et al., 1990).

As mentioned above, the combination of vascular permeability and HA build up in the lungs could produce a hydrogel that significantly inhibits gas exchange in bronchoalveolar spaces. This is consistent with the autopsy reports of hyaline membranes in the lungs of deceased COVID-19 patients as well as other acute respiratory distress conditions (e.g., SARS, MERS, ARDS) (Barton et al., 2020; Xu et al., 2020; Adachi et al., 2020) Although this likely represents a late-stage event in severe cases of COVID-19, if the cause is overproduction of HA as a result of disruption of the RAS, it is also a potentially valuable intervention point because the condition is easily identified, and treatment could have rapid and significant beneficial effects.

In addition, increased levels of the vasodilating peptide APLN that are produced in COVID-19 patients could have spillover effects on cardiac function. APLN upregulates the expression of ACE2 (Sato et al., 2013) and directly affects cardiac contraction and vasodilation. Increased levels of APLN are known to be associated with cardiac arrhythmia (Salska et al., 2018) and in the case of hyper-stimulated BK output, could be causing cardiac events in COVID-19 patients. In addition, increased levels of APLN could lead to more ACE2 receptors for SARS-CoV-2 in the heart and thus stimulate further infection.

Furthermore, excess BK can lead to hypokalemia (Zhang et al., 2018), which is associated with arrhythmia and sudden cardiac death (Kjeldsen, 2010), (Bielecka-Dabrowa et al., 2012; Skogestad and Aronsen, 2018), both of which have been reported in COVID-19 patients (Huang et al., 2020; Guo et al., 2020), (Wang et al., 2020); a recent report confirms that hypokalemia is

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occurring in severe cases of COVID-19 (Lippi et al., 2020). It is also notable that many of the other symptoms being reported for COVID-19 (myalgia, fatigue, nausea, vomiting, diarrhea, anorexia, headaches, decreased cognitive function) are remarkably similar to other hyper-BKconditions that lead to vascular hyper-permeabilization such as angioedema as was recently noted (van de Veerdonk et al., 2020). In agreement with that report, our results indicate that the pathology of COVID-19 is likely the result of Bradykinin Storms rather than cytokine storms (although given the induction of IL2 by BK, the two may be intricately linked). This model predicted that a loss of ACE2 would exacerbate the BK-induced pathogenesis (van de Veerdonk et al., 2020). However, the BAL fluid expression data indicate that the Bradykinin Storm is instead caused by upregulation of ACE2 and reduced degradation of BK by ACE. Based on this datadriven model, an individual's symptomatology is likely directly related to the specific tissue distribution of viral infection around the body (Figure 4) and should be viewed in the context of an overactive bradykinin response. The majority of circulating BK is degraded in the lungs by ACE and therefore heterogeneous symptoms of COVID-19 could also be the result of systemic effects of increased levels of circulating bradykinin and the eight-fold reduction of ACE in the lung microvasculature that would normally degrade it.

Figure 4

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Systemic-level effects of critically imbalanced RAS and BK pathways.

The gene expression patterns from COVID BAL samples reveal a RAS that is skewed toward low levels of ACE that result in higher levels of Ang1-9 and BK. High levels of ACE normally present

Given this model, factors that affect RAS balance should be further investigated in the framework of diagnosis and treatment. For example, another well-documented regulator of RAS is Vitamin D (Vaidya and Williams, 2012) as the liganded Vitamin D receptor (VDR) suppresses REN expression. Patients who are deficient in Vitamin D are at-risk for ARDS in general (Dancer et al., 2015) and Vitamin D deficiencies have recently been associated with severity of illness in COVID-19 patients (Alipio, 2020). Our BAL gene expression analysis shows that VDR is 2-fold down-regulated and enzymes [CYP24A1 (465 fold), CYP3A4 (208 fold)] that catabolize Vitamin D (1,25(OH)2D) and its precursor (25OHD) (Bikle, 2014) are up-regulated in COVID-19 patients compared to controls, which will likely result in further increases in REN. Furthermore, our analysis of ChipSeq experiments from a VDR study Tuoresmäki et al., 2014 have determined that, in addition to REN, the following genes in the RAS-Bradykinin system have a VDR binding site within 20 kilobases: BDKRB1, BDKRB2, CYP24A1, DPP4, IKBKG (regulates NFkappaB), KLK1, KLK2, KLK4, KLK6, KLK7, KLK9, KLK10, and MME. Six of these binding sites can be tied to the following genes via chromatin structure with the use of H-MAGMA and Hi-C data (see Materials and methods): DPP4, BDKRB2, KLK6, KLK7, KLK10, and IKBKG. VDR binds to many sites in the genome with tissue-specific binding patterns so these putative associations to other genes in the RAS and BK pathways will require further investigation.

Potential interventions

Several interventional points (most of them already FDA-approved pharmaceuticals) could be explored with the goal of increasing ACE, decreasing BK, or blocking BK2 receptors (Table 1). Icatibant is a BKB2R antagonist (Dubois and Cohen, 2010) whereas Ecallantide acts to inhibit KLKB1, reducing levels of BK production (Farkas and Varga, 2011). Androgens (danazol and stanasolol) increase SERPING1, although the side effects likely make these undesirable (Wilkerson, 2012), but recombinant forms of SERPING1 (Berinert/Cinryze/Haegarda) could be administered to reduce BK levels. It should be noted that any intervention may need to be timed

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correctly given that REN levels rise on a diurnal cycle (Gordon et al., 1966), peaking at 4AM which corresponds with the commonly reported worsening of COVID-19 symptoms at night. Another approach would be the modulation of REN levels via Vitamin D supplementation when warranted. 4-methylumbelliferone (Hymecromone) is a potent inhibitor of HAS1, HAS2, and HAS3 gene expression and results in the suppression of the production of hyaluronan in an ARDS model (McKallip et al., 2003; McKallip et al., 2013). Hymecromone (4-methylumbelliferone) is approved for use in Asia and Europe for the treatment of biliary spasm. However, it can cause diarrhea with subsequent hypokalemia, so considerable caution should be used if this were to be tried with COVID-19 patients (NCATS Inxight, 2020). As mentioned above, Timbetasin may reduce COVID-19 related coagulopathies by increasing fibrinolysis.

Table 1 Potential therapeutic interventions, their targets, and predicted effect.

Drug	Target	Predicted Effect
Danazol, Stanozolol	SERPING1	Reduce Bradykinin production
Icatibant	BKB2R	Reduce Bradykinin signaling
Ecallantide	KLKB1	Reduce Bradykinin production
Berinert,Cinryze,Haegarda	SERPING1	Reduce Bradykinin production
Vitamin D	REN	Reduce Renin production
Hymecromone	HAS1,HAS2, HAS3	Reduce hyaluronan
Timbetasin	TMSB4X	Increase fibrinolysis

The testing of any of these pharmaceutical interventions should be done in well-designed clinical trials. Given the likely future outbreaks of zoonotic viruses with a similar outcome, it would be in the best interest long-term to invest in the development of small molecules that can inhibit the virus from replicating or suppressing the host immune system such as a 3CLpro inhibitor. However, to date, no large multi-centered, randomized, placebo controlled, blinded clinical trials have been done with 3CLpro inhibitors (Sisay, 2020). In the meantime, our analyses suggest that prevention and treatment centered on vascular hyper-permeability and the suppression of hyaluronan may prove beneficial in fighting the pathogenesis of COVID-19. Given the fact that two recent studies have validated our model's predictions of hypokalemia (Lippi et al., 2020) and Vitamin D deficiency (Alipio, 2020) in COVID-19 patients, we suggest that rapid testing of the pharmaceutical interventions discussed above is warranted.

Decision letter

- Frank L van de Veerdonk Reviewing Editor; Radboud University Medical Center, Netherlands
- Jos WM van der Meer Senior Editor; Radboud University Medical Centre, Netherlands
- Frank L van de VeerdonkReviewer; Radboud University Medical Center, Netherlands
- Roger Little Reviewer

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In the interests of transparency, eLife publishes the most substantive revision requests and the accompanying author responses.

Acceptance summary:

The manuscript has highlighted a core response in COVID-19 with RAS and bradykinin which is really a different signature than any other viral pneumonia other than coronavirus infection. This supports the importance of these pathways in coronavirus and contributes to a better understanding of COVID-19. The novelty and importance is also the site of infection (the lungs) that has been studied for this signature which really adds novelty to the existing literature.

Decision letter after peer review:

Thank you for submitting your article "A Mechanistic Model and Therapeutic Interventions for COVID-19 Involving a RAS-Mediated Bradykinin Storm" for consideration by eLife. Your article has been reviewed by three peer reviewers, including Frank L van de Veerdonk as the Reviewing Editor and Reviewer #1, and the evaluation has been overseen by Jos van der Meer as the Senior Editor. The following individual involved in review of your submission has agreed to reveal their identity: Roger Little (Reviewer #3).

The reviewers have discussed the reviews with one another and the Reviewing Editor has drafted this decision to help you prepare a revised submission.

We would like to draw your attention to changes in our revision policy that we have made in response to COVID-19 (https://elifesciences.org/articles/57162). Specifically, we are asking editors to accept without delay manuscripts, like yours, that they judge can stand as eLife papers without additional data, even if they feel that they would make the manuscript stronger. Thus the revisions requested below only address clarity and presentation.

Summary:

The authors have used a systems biology approach and analyzed data from BAL (9 COVID patients) with 40 control BALs. They clearly demonstrate a signature of a dysregulated RAAS and KKS. Further analysis shows the signature is skewed towards an incapacity to dampen the KKS and bradykinin production that might lead to a bradykinin storm that could contribute to the endothelial dysfunction that results in vascular leakage seen in the early stages of patients admitted to the hospital with COVID. The data are timely, conclusions supported by the data and the BAL sample analysis provides real novel data.

Figure 2: Please designate Figure 2 into two panels: A and B, since it is later referred to in this way in the text. It would also be helpful to illustrate the scale so one can observe the large disruption of the system. The scale only goes to 5 in both directions, and being able to see the extreme overexpression would improve the argument that components of the BK system are overexpressed.

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Subsection "Hyaluronic Acid Synthesis and Degradation". It would be helpful to add a sentence of two to expand on the pulmonary thrombosis evidence, as it's known that thrombosis is observed in some Covid-19 patients. It could possibly be added in the third paragraph below.

Subsection "Bradykinin Storms: A Model of SARS-CoV-2, COVID-19, and BK-driven Vascular Permeabilization" third paragraph. The HA hypothesis is compelling and potentially explanatory for the hypoxia observed in Covid-19 patients. This hypothesis would be better supported by a representation of the data referenced here (Barton et al., 2020; Xu et al., 2020; Adachi et al., 2020), as opposed to just stating that HA buildup is observed. Either a discussion or even a table would be useful with referenced data.

Same section paragraph five. Here again, it would be useful to represent the studies mentioned here (van de Veerdonk et al., 2020) with similar phenotypic observations to Covid-19. Additional discussion of the data from that paper, or even better the addition of a table with referenced data is suggested. The BK hypothesis is a strong and central hypothesis of this paper and it would be better supported with more than just a statement and a reference.

The results of the ChipSeq analysis should be further described. Most importantly, what is the significance of the binding site within 20 kilobases? It seems like a lot of genomic real estate to make an assertion that there is some effect. Is there any evidence this proximity results in activation or deactivation? If so please provide a reference.

Subsection "Potential Interventions": Another suggestion here to include a table with suggested interventions -> targets -> drugs -> expected effects.

Supplementary figures S1 and S2 could be represented by single tables and also made available in xls forms.

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The world will be fighting coronavirus for the next three to four years as virus hot spots skip from nation to nation, and the pandemic's toll will linger for decades, said Dr. Larry Brilliant, a California epidemiologist who was part of a World Health Organization team in the 1970s that helped eradicate smallpox.

But it's "not all doom and gloom," with effective vaccines likely to emerge from dozens of candidates worldwide and effective treatments, including convalescent plasma and monoclonal antibodies, to help people recover more quickly, said Brilliant, who chairs Ending Pandemics advisory board.

"We will still be chasing the virus four years from now. But it won't be like (today)," Brilliant told the USA TODAY Editorial Board on Monday afternoon. "It will be like the smallpox eradication program. The polio eradication program. Having yellow fever in some countries and not in others."

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Hospitalized Covid-19 patients who received transfusions of blood plasma rich with antibodies from recovered patients reduced their mortality rate by about 50%, according to researchers running a large national study.

The researchers presented their data analysis Saturday in a webinar for physicians interested in learning about so-called convalescent plasma, with data slides that were reviewed by The Wall Street Journal. The researchers said they saw signs that the treatment might be working in patients who received high levels of antibodies in plasma early in the course of their illness. They based their conclusions on an analysis of about 3,000 patients.

Patients who at three days or less after diagnosis received plasma containing high levels of antibodies against the coronavirus had a mortality rate of 6.6% at seven days after the transfusion. That compared with a mortality rate of 13.3% for patients who got plasma with low levels of antibodies at four days or more after diagnosis. That indicates reduced mortality of about 50%, the researchers said.

At 30 days after transfusion, the mortality rate was reduced by about 36%, investigators reported

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In conclusion, the current study suggests that CP use in severe and critically ill patients with COVID-19 may improve survival if given early in the course of disease. The efficacy as a

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potential therapy needs further study in well-designed trials to better understand the contribution of CP to outomes in COVID-19.

539) 2020-08-06 Bloch EM: Convalescent plasma to treat COVID-19. Convalescent plasma to treat COVID-19. Blood 6 August 2020; 136 (6): 654-655. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414591/pdf/main.pdf

In conclusion, observational studies and compassionate use programs have been instrumental in the mobilization of CCP to contend with a global health emergency. Although safety has been addressed, efficacy data are critically needed to transition CCP's status from an investigational product to a standard therapy. The latter has practical ramifications, offering a formal mechanism for reimbursement and thus durable treatment strategy. Broadly, COVID-19 presents a rare opportunity to study CP. If shown to be effective, CP would offer a scalable model that could be applied both to the current pandemic as well as to future emerging infectious diseases. It could also facilitate development of hyperimmune globulin and vaccine design. Clinical trials are already under way to address the uncertainty of use. Nonetheless, harmonization of efforts is needed along with creative approaches to overcome looming obstacles, such as pairing of trials of similar design and/or metanalysis. We must not be left wondering whether the intervention worked after the pandemic wanes.

540) 2020-08-06 Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, Li J, Wang Z, Wu W, Wu M, Li W, Li L, Cai Y, Bosco B, Zhong A, Liu X, Lv T, Gan Z, Chen G, Pan Y, Liu C, Zhang K, Xu X, Wang C, Wang Q: Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood 6 August 2020; 136 (6): 755-758. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414593/pdf/main.pdf

Experience from SARS-CoV-1 shows that convalescent plasma is most effective when administered shortly after symptom onset, typically within 2 weeks.7,14,17 The study by Liu et al¹⁶ showed that the effect of CCP was similar in an interval of 3 weeks' duration of symptoms. We compared the time to clinical improvement in patients with different therapy timings in our cohort, including 1 to 4 weeks, 5 to 6 weeks, 7 weeks, and \$8 weeks after symptom onset. The results showed that the median time to clinical improvement was ;10 days in the 1 to 4 weeks', 5 to 6 weeks', and 7 weeks' groups. However, the time to clinical improvement was significantly prolonged in the \$8 weeks' group (Figure 1I).

In summary, we analyzed a large cohort of patients with COVID19 who received CCP and provide detailed evidence regarding their clinical improvement. Although the homogeneous data obtained from a single center may reduce some biases, there could inevitably be some confounding factors (eg, biased patient assignments) in this retrospective study. In addition, complete data on neutralizing antibody titers in CCP units were not available, limiting the power of evaluating the correlation between the quality of donor plasma and efficacy. Moreover, a stratified analysis of cases of severe and critical patients could not be performed due to the low proportion of critical patients. This analysis differs from existing studies in that its dynamic laboratory observations using large-scale data make it possible to analyze the potential therapeutic mechanism of CCP, recognize the characteristics of responders and nonresponders, and identify the indications and timing of therapy.18 Our results suggest that CCP, transfused even after 2 weeks (median of 45 days in our cohort) of symptom onset, could improve the symptoms and mortality in patients with severe or critical cases of COVID-19. We anticipate that this study could shed new light in clinical practice and monoclonal antibody development for COVID-19.

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2020-08-06. Tobian AA, Shaz BH: Earlier the better: convalescent plasma. Blood 6 August 2020; 136 (6): 652-653.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414595/pdf/main.pdf

Convalescent plasma is one of the best therapies currently available to treat COVID-19. However, critical questions on timing of treatment in the disease course and dose (volume and antibody titer levels) need to be answered. These answers will also help prepare us for other passive antibody treatments (eg, hyperimmune globulin made from convalescent plasma and monoclonal antibodies). The medical community must work together to battle this deadly disease in order to determine the best therapies and reduce mortality.

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- 543) 2020-08-12 Kozlov M: Two Washington U. doctors lead national effort to study new COVID-19 treatment. St. Louis Post-Dispatch Aug 12, 2020. https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctorslead-national-effort-to-study-new-covid-19-treatment/article ccec0f56-4493-5a26-8601-45e35d364b2d.html

Since April, the Trump administration has set aside more than \$300 million to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving high-risk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

Moreover, clinical trials require thousands of patients, but the virus is spiking so quickly in communities, by the time doctors set up a trial, patients have disappeared.

544) 2020-08-12 Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Soto JCD, Baker SE, Shepherd JRA, van Helmond N, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whenlan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather DL, Wright RS, Carter RE, Casadevall A: Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: Initial three-month experience. Version 1. medRxiv Preprint. 2020 Aug 12.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7430623/?report=printable

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Abstract ...Participants: Adult participants enrolled and transfused under the purview of the US Convalescent Plasma EAP program between April4 and July 4, 2020 who were hospitalized with (or at risk of) severe or life threatening acute COVID-19 respiratory syndrome. Intervention: Transfusion of at least one unit of human COVID-19 convalescent plasma using standard transfusion guidelines at any time during hospitalization. Convalescent plasma was donated by recently-recovered COVID-19 survivors, and the antibody levels in the units collected were unknown at the time of transfusion. Main Outcomes and Measures: Seven and thirty-day mortality. Results: the 35,322 transfused patients had heterogeneous demographic and clinical characteristics. This cohort included a high proportion of critically-ill patients, with 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion. The seven-day mortality rate was 8.7% [95% CI 8.3-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis (p <0.0001).

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- **549)** 2020-08-20 Pharmaceutical Technology: Roche teams up with Regeneron on Covid-19 therapy. https://www.pharmaceutical-technology.com/news/roche-regeneron-covid-therapy/
- 550) 2020-08-21 Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, Fulton BO, Yan Y, Koon K, Patel K, Chung KM, Hermann A, Ullman E, Cruz J, Rafique A, Huang T, Fairhurst J, Libertiny C, Malbec M, Lee W, Welsh R, Farr G, Pennington S, Deshpande D, Cheng J, Watty A, Bouffard P, Babb R, Levenkova N, Chen C, Zhang B, Romero Hernandez A, Saotome K, Zhou Y, Franklin M, Sivapalasingam S, Chien Kye D, Weston S, logue J, Haupt R, Frieman M, Chen G, Olson W, Murphy AJ, Stahl N, Yancopoulos GD, Kyratsous CA: Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody

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cocktail. Science 2020; 369 (6506): 1010-1014. https://science.sciencemag.org/content/369/6506/1010

551) 2020-08-23 Trump D: Donald Trump August 23 White House COVID-19 Press Conference Transcript. Rev Aug 23, 2020. Video of the conference:

https://www.youtube.com/watch?v=nE0EkrElCRk Transcript:

https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript

Appendix 1 of a draft cover letter (never sent) to the President Biden of August 2021:

Transcript of August 23, 2021 White House press conference in its entirety: https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript

(The video of the August 23, 2020 White House press conference in its entirety: https://www.youtube.com/watch?v=nE0EkrElCRk)

President Donald Trump held an August 23 coronavirus press conference where he announced the FDA is issuing an emergency authorization for a COVID-19 treatment called convalescent plasma. Trump touted the approval as a "historic announcement." Read the full transcript of the press conference here.

Donald Trump: (01:38)

Thank you very much, and it's good to see you all. Hope you had a great weekend at your convention. We're going to have a great convention coming up, and I look forward to it.

Donald Trump: (01:51)

But before I discuss a very historic breakthrough in our fight against the China virus, I'd like to provide an update on the recent wildfires in California and the storms in the Gulf of Mexico. Yesterday, I approved a major disaster declaration for California, spoke to Governor Newsom as they battled two of the worst wildfires in the history of their state. That continues.

Donald Trump: (02:19)

The federal government has already deployed over 26,000 first responders and personnel to battle the wildfires. We're working very closely with the Governor and very closely with a lot of great state representatives and local representatives. We'll take care of the situation, but we have 26,000 first responders already. Our hearts go out to the thousands of families who have lost their homes, as we grieve for the families of two first responders and five residents who have tragically lost their lives in a very horrific fire, one of the biggest we've ever seen.

Donald Trump: (<u>03:01</u>)

My administration is also closely monitoring Hurricane Marco and Tropical Storm Laura, which are coming in rapidly. Hurricane Marco is expected to make landfall in Louisiana tomorrow, and Tropical Storm Laura is expected to hit Louisiana two days later. This is somewhat unprecedented, the scope of the storms, and also the fact that they come so quickly after one another. Both storms have the potential of gathering strength before they make landfall and could cause significant damage across the Gulf Coast and also in Puerto Rico. We have everybody stationed and ready to go in Puerto Rico and the Gulf Coast. We

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have tremendous, tremendous people. FEMA is lined up. We have the Coast Guard ready. The Coast Guard has done a fantastic job. They do such good work, and we want to thank our great Coast Guard.

Donald Trump: (03:58)

I'm asking all Americans in the storm's path to follow the instructions of your state and local governments very closely. I've approved emergency declarations for Puerto Rico and for Louisiana. FEMA is mobilized on the ground and is ready to help. They will be in there very quickly, very, very quickly. I spoke to Governor John Bel Edwards also of Louisiana, and I've informed him, and at his request also, a major disaster declaration is signed and ready to go. We have everybody ready in Puerto Rico, the Gulf Coast, Louisiana, and also on the forest fires in California. We have a great team. Unfortunately, we have some very, very powerful natural disasters.

Donald Trump: (04:47)

On the therapeutics front, this is what I've been looking to do for a long time. This is a great thing. Today, I'm pleased to make a truly historic announcement in our battle against the China virus that will save countless lives. The FDA has issued an Emergency Use Authorization, and a that's such a powerful term, Emergency Use Authorization, for a treatment known as convalescent plasma. This is a powerful therapy that transfuses very, very strong antibodies from the blood of recovered patients to help treat patients battling a current infection. It's had an incredible rate of success. Today's action will dramatically expand access to this treatment.

Donald Trump: (05:39)

I want to thank Dr. Hahn and Secretary Azar. I want to thank the FDA, all of the people that have been working very hard on this. It showed tremendous potential. It's only made possible because of Operation Warp Speed. That is everybody working together. We're years ahead of approvals that we would be if we went by the speed levels of past administration. We'd be two years, three years behind where we are today, and that includes on vaccines that you'll be hearing about very soon, very shortly.

Donald Trump: (06:16)

To deliver treatments and vaccine to save lives, we're removing unnecessary barriers and delays, not by cutting corners, but by marshaling the full power of the federal government. We provided \$48 million to fund the Mayo Clinic study that tested the efficacy of convalescent plasma for patients with the virus. Through this study over 100,000 Americans have already enrolled to receive this treatment, and it is proven to reduce mortality by 35%. It's a tremendous number. The FDA, MIT, Harvard, and Mount Sinai Hospital have also found convalescent plasma to be a very effective method of fighting this horrible disease. Based on the science and the data, the FDA has made the independent determination that the treatment is safe and very effective.

Donald Trump: (07:12)

Recently, we provided up to \$270 million to the American Red Cross and America's blood centers to support the collection of up to 360,000 units of plasma. In late July, we launched a nationwide campaign to ask patients who have recovered, and these are patients that have been incredible the way they've donated. But these are people recovered from the virus to donate plasma. Since then, weekly plasma donations have doubled. Today, I once again urge all Americans who have recovered from the virus to go to coronavirus.gov and sign up and donate plasma today, please. It's been really an incredible ... Just incredible people. The country has united so strongly behind this.

Donald Trump: (<u>08:08</u>)

I'll go over the numbers, but if you look at what's happened and the success that we've had that people don't talk about, the United States has experienced the lowest case fatality rate of any major country in the world. You don't hear that. The European Union's case fatality

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rate is estimated to be three times higher than that in the United States. Europe has seen 33% more fatalities compared to a typical non-pandemic year than the United States.

Donald Trump: (08:38)

I just want to ask two of our people that have done such a fantastic job, Alex Azar and Stephen Hahn to say a few words. Stephen, I want to thank you because the FDA really stepped up and especially over the last few days in getting this done. The results have been incredible, and I think you'll see the results even go up very substantially. So we appreciate it. And maybe I'll ask Alex to go first, and then Stephen. Thank you very much, Alex.

Alex Azar: (09:06)

Well, thank you very much, Mr. President. Thanks for the bold leadership that allowed us to deliver this very happy news today. Thanks to your all-of-America approach, America has done more than any other country to expand the arsenal that we have to battle COVID-19. Thanks to early efforts by your administration, Americans have broader access to these treatments, including convalescent plasma, than patients anywhere else in the world.

Alex Azar: (09:33)

In early April, early in our fight against COVID-19, the FDA, BARDA, the Mayo Clinic, and other partners sprang into action to set up an expanded access protocol for this promising treatment. President Trump is the right-to-try President, and he's fought hard to ensure that Americans can have access to promising COVID-19 treatments. Convalescent plasma has been a tried-and-true therapeutic method in prior outbreaks, but the President wanted to ensure that we develop the data to support its use. This FDA authorization is one result of that effort.

Alex Azar: (10:06)

The data we gathered suggests that patients who were treated early in their disease course, within three days of being diagnosed with plasma containing high levels of antibodies, benefited the most from treatment. We saw about a 35% better survival in the patients who benefited most from the treatment,

which were patients under 80, who were not on artificial respiration. I just want to emphasize this point because I don't want you to gloss over this number. We dream in drug development of something like a 35% mortality reduction. This is a major advance in the treatment of patients. This is a major advance.

Alex Azar: (10:51)

Convalescent plasma is one new tool that we've added to our arsenal against COVID-19 alongside remdesivir, steroids, and a number of other promising options currently being studied. Because of the President's Operation Warp Speed, we expect to have other new results and new options reaching patients as soon as this fall. Operation Warp Speed is supporting experimental therapeutics all the way through to manufacturing, so that if they meet FDA's gold standard for safety and efficacy, they can begin reaching patients without a day wasted.

Alex Azar: (11:24)

Americans who have tested positive for and recovered from COVID-19 can go to coronavirus.gov to find out a quick, convenient way to play a potentially lifesaving role in our fight. Know if you donate plasma, you could save a life. We've also provided guidance, so healthcare providers can contact patients who have recovered from COVID-19 and give them information on how they can donate.

Alex Azar: (11:48)

So thank you again, Mr. President for supporting this remarkable progress against COVID-19, and I want to thank Dr. Hahn, Dr. Marks, and the entire team at the FDA for the speed

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with which they've approached this, the diligence to ensure that this meets the standards at FDA. I'll turn it over to Dr. Hahn, if it's okay, Mr. President.

Donald Trump: (<u>12:07</u>)

[crosstalk 00:12:07] thank you very much. Please, Doctor?

Dr. Hahn: (12:09)

Dr. Hahn: (12:10)

Thank you, Mr. President-Donald Trump: (12:10) [crosstalk 00:12:10].

... for your leadership. It's good to be here today to announce FDA's recent decision. From the beginning of this pandemic, the President has asked FDA to cut back red tape to try to speed medical products into the hands of providers, patients, and American consumers. I just want to echo the President's thanks to the more than the 17,000 men and women who work at FDA. They have worked day and night to, in fact, do that.

Dr. Hahn: (12:36)

Plasma is the liquid portion of the blood. That liquid portion contains the natural immunity that someone develops in response to an infection, in this case COVID-19. That liquid portion can be extracted. And for many years, as the President and Secretary Azar said, has been given to patients with infectious diseases for more than a hundred years. So there was a really good rationale for why this might work. In fact, as was mentioned, in early April, an expanded access program was started at the Mayo Clinic with the support of the federal government under President Trump's leadership. That has gone on for the last four months. More than 90,000, close to 100,000, Americans have enrolled in this program, and over 70,000 have received treatment. This is one of the largest expanded access programs in the history of FDA. So a very successful approach to evaluating how convalescent plasma would work.

Dr. Hahn: (13:34)

In the independent judgment of experts and expert scientists at FDA who have reviewed the totality of data, not just the data from this expanded access program, but more than a dozen published studies, as well as the historical experience associated with this, those scientists have concluded that COVID-19 convalescent plasma is safe and shows promising efficacy, thereby meeting the criteria for an emergency use authorization. In the optimal patients, as described by secretary Azar, treated with convalescent plasma at the highest titers, there was a 35% improvement in survival, which is a significant clinical benefit. Now, we're waiting for more data. We're going to continue to gather data, but this clearly meets the criteria that we've established for emergency use authorization, and we're very pleased with these results.

Dr. Hahn: (14:27)

Let me just put this in perspective. Many of you know I was a cancer doctor before I became FDA commissioner, and a 35% improvement in survival is a pretty substantial clinical benefit. What that means is, and if the data continue to pan out, 100 people who are sick with COVID-19, 35 would have been saved because of the administration of plasma. We've seen a great deal of demand for this from doctors around the country. What this emergency use authorization today does, it allows us to continue that and meet the demand.

Dr. Hahn: (15:00)

Again, I want to echo the President's and the Secretary's ask of the American people. If you've recovered from COVID-19, please donate. It could save a life. Mr. President, thank you again.

Donald Trump: (15:11)

Thank you very much, Stephen. I appreciate it.

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Speaker 6: (15:18) Mr. President?

Donald Trump: (15:19) Okay, any questions?

Speaker 6: (15:19) Mr. President? Mr. President?

Speaker 7: (15:19)

Thank you, Mr. President. I want to first ask you about the COVID-19 drugs that are in phase three.

Donald Trump: (15:23) [crosstalk 00:15:24].

Speaker 7: (15:24)

Are they going to be available to the American population on ... You and I talked previously about this idea of right to try.

Donald Trump: (15:32)

Right.

Speaker 7: (15:33)

Can we assure the American people that if it's being studied and it's in phase three, you have that right?

Donald Trump: (15:38)

That's a great question, and I'm not sure a lot of people have been thinking about right to try. We're all waiting for the final answer. Maybe I could ask Stephen, but I would say that right to try is exactly ... If somebody is virtually terminal, in other words they're not going to make it, and if we have these incredible therapies and drugs that are happening, Alex, I think it's a very interesting question. I congratulate you for that question because I think we're-

Speaker 7: (<u>16:05</u>) Thanks, Mr. President.

Donald Trump: (16:05)

... all waiting for that exact final endpoint. What about that, Stephen? We have all of these seemingly great answers that are ready to come out, but because of the process, it takes a little- Can we use some of this early under Right to Try? Please.

Dr. Hahn: (16:18)

So it's a really good question. Of course, it all depends on the clinical circumstances and what a doctor and a patient together decide with respect to the administration of any agent.

Dr. Hahn: (16:29)

But if you think about what happened with convalescent plasma and the expanded access program, this is exactly what happened. We have ongoing clinical trials that are randomized between placebo or an inactive substance and the convalescent plasma. While that was going on, we knew that there was great demand from patients and doctors. The expanded access program is a way of actually doing that and fits perfectly with what the President just said

about allowing people to be able to use something that we have now determined

to be very safe.

Donald Trump: (16:57)

I think it was something we have to really consider very strongly.

Dr. Hahn: (17:00)

Yes, sir.

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Donald Trump: (17:00)

I think it's fantastic. You should get credit for that.

Speaker 7: (<u>17:04</u>) Thanks, Mr. President. Donald Trump: (17:04) Thank you. That's very good.

Speaker 8: (<u>17:04</u>) Mr. President?

Donald Trump: (17:04)

Please, in the back. [OEN 00:17:08]?

Speaker 9: (<u>17:10</u>)

Thank you Mr. President. Convalescent plasma as a treatment has been around for nearly a hundred years. You mentioned Operation Warp Speed, which enabled this process to move along a lot faster. What went into the effort for this to be approved for COVID-19? And was that holdup political in nature?

Donald Trump: (17:30)

Well, I think that there might have been a holdup, but we broke the logjam over the last week, to be honest. I think that there are people in the FDA and actually in your larger department that can see things being held up and wouldn't mind so much. That's my opinion, a very strong opinion. And that's for political reasons. This has nothing to do with politics. This has to do with life or death. So we are being very strong, and we are being very forthright. We have got some incredible answers, and we're not going to let them be held up because every day is lives, and we're not going to let that happen. Okay? Very good, thank

Speaker 10: (18:06) Mr. President?

Donald Trump: (18:06) Please, go ahead.

Speaker 11: (18:10)

Mr. President, in announcing this today, you said that the FDA has made the independent determination that the treatment is **safe** and very effective. Yet Dr Hahn just said it was showing promising efficacy. Which of the two is correct?

Donald Trump: (18:25)

Well, I think I'll let Dr. Hahn answer that question.

Dr. Hahn: (18:29)

Under our legal authority for Emergency Use Authorization, this is not the same as an approval, but it's an authorization, and it allows us to expand the access to this. We know we're going to continue to collect data. We knew that for all of our Emergency Use Authorizations.

Dr. Hahn: (18:44)

So, for example, remdesivir, which was approved or authorized on May 1st, we're still collecting data, and we will continue to do that with plasma as well. So it's the nuances of the language around the authorization that we use and the legal aspect too.

Speaker 11: (18:57)

It's a promising treatment. You couldn't say it's very effective just yet.

Dr. Hahn: (19:02)

If you're one of those 35 out of 100 people who these data suggest or show survive as a result of it, this is pretty significant for that person and their family.

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Donald Trump: (19:12)
Okay, this is a very big day. It's a day we've been looking forward to. Thank you very much. Great questions.

Speaker 12: (19:18)
Was there pressure on you, Dr. Hahn, to authorize this?

Speaker 13: (19:18)
Dr. Hahn?

Speaker 14: (19:18)
Mr. President [crosstalk 00:19:19]

Speaker 12: (19:19)
Dr. Hahn. Could you answer that question? [crosstalk 00:19:19] Dr. Hahn, to authorize this.

Speaker 12: (19:21)
(silence)
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552) 2020-08-23 Hahn S: Dr. Hahn discussing convalescent plasma at White House News conference. https://www.facebook.com/FDA/videos/dr-hahn-convalescent-plasma-eua/350991072605290/ goes directly to Dr. Hahn's words that follow are extremely important because of what resulted:

By stating that the data was not just from the Mayo Clinic/(FDA) expanded access program as you will note below, Dr. Hahn justified that the issuing of the EUA was completely appropriate. But, in so doing, availability of COVID-19 convalescent plasma from any of the previous Expanded Access Programs was now *de facto* completely suspended / interrupted.

So, in the independent judgment of experts and expert scientists at FDA, who have reviewed the totality of data – not just the data from this expanded access program but more than a dozen published studies as well as the historical experience associated with this – those scientists have concluded that COVID-19 convalescent plasma is safe and shows promising efficacy thereby meeting the criteria for an emergency use authorization.

553) 2020-08-23 Hinton DM: U.S. Food & Drug Administration Emergency Utilization Authorization (EUA) Letter to Robert P. Kadlec, MD, MTM&H, MS, Assistant Secretary for Preparedness and Response, issuing the EUA on COVID-19 Convalescent Plasma, August 23, 2020.

https://web.archive.org/web/20200823220439/https://www.fda.gov/media/141477/download

Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of disease. COVID-19 convalescent plasma units containing antibodies to SARS-CoV-2 but not qualified as high-titer by a test found acceptable for this purpose by FDA (see Section II) are considered Low Titer units by a test found acceptable for this purpose by FDA (see Section II) are considered Low Titer units and are acceptable for use based on an individual assessment of patient benefit-risk....

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554) 2020-08-23 FDA News Release: FDA issues emergency use authorization for Convalescent Plasma as potential promising COVID-19 treatment, another achievement in Administration's fight against pandemic. U.S. Food & Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency's ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its <u>decision memorandum</u>, this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.

Today's action follows the FDA's extensive review of the science and data generated over the past several months stemming from efforts to facilitate emergency access to convalescent plasma for patients as clinical trials to definitively demonstrate safety and efficacy remain ongoing.

The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19.

Alex Azar, Health and Human Services Secretary:

"The FDA's emergency authorization for convalescent plasma is a milestone achievement in President Trump's efforts to save lives from COVID-19," said Secretary Azar. "The Trump Administration recognized the potential of convalescent plasma early on. Months ago, the FDA, BARDA, and private partners began work on making this product available across the country while continuing to evaluate data through clinical trials. Our work on convalescent plasma has delivered broader access to the product than is available in any other country and reached more than 70,000 American patients so far. We are deeply grateful to Americans who have already donated and encourage individuals who have recovered from COVID-19 to consider donating convalescent plasma."

Stephen M. Hahn, M.D., FDA Commissioner:

"I am committed to releasing safe and potentially helpful treatments for COVID-19 as quickly as possible in order to save lives. We're encouraged by the early promising data that we've seen about convalescent plasma. The data from studies conducted this year shows that plasma from patients who've recovered from COVID-19 has the potential to help treat those who are suffering from the effects of getting this terrible virus," said Dr. Hahn. "At the same time, we will continue to work with researchers to continue randomized clinical trials to study the safety and effectiveness of convalescent plasma in treating patients infected with the novel coronavirus."

Scientific Evidence on Convalescent Plasma

Based on an evaluation of the <u>EUA criteria</u> and the totality of the available scientific evidence, the FDA's Center for Biologics Evaluation and Research determined that the statutory criteria for issuing an EUA criteria were met.

The FDA determined that it is reasonable to believe that COVID-19 convalescent plasma may be effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients. The agency also determined that the known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product and that there are no adequate, approved, and available alternative treatments.

The EUA is not intended to replace randomized clinical trials and facilitating the enrollment of patients into any of the ongoing randomized clinical trials is critically important for the definitive demonstration of safety and efficacy of COVID-19 convalescent plasma. The FDA continues to recommend that the designs of ongoing randomized clinical trials of COVID-19 convalescent plasma and other therapeutic agents remain unaltered, as COVID-19 convalescent plasma does not yet represent a new standard of care based on the current available evidence.

The EUA remains in effect until the termination of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19. The EUA may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.

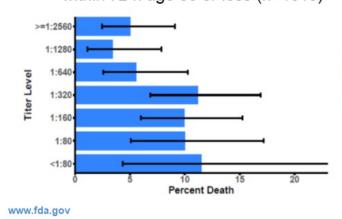
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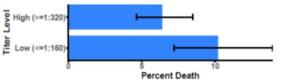
COVID-19 Convalescent Plasma Reduction in Death at 7 Days



Non-intubated patients treated within 72 h age 80 or less (n=1018)



Statistically significant 37% reduction in mortality in those treated with high titer convalescent plasma (p=.03)



High titer corresponds approximately to Ortho VITROS S/C level ≥ 12

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products

555) 2020-08-23 U.S. Food & Drug Administration: Clinical Memorandum. COVID-19 Convalescent Plasma EUA Decision Memo. https://www.fda.gov/media/141480/download is the baseline URL which when placed in the Wayback Machine, 8-23-2020 to 2-2021 is the same memo on CCP EUA issued 8-23-2020: https://www.fda.gov/media/141480/download

556) 2020-08-23 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. August 23, 2020.

https://web.archive.org/web/20200901081726/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

557) 2020-08-23 U.S. Food & Drug Administration: Donate COVID-19 Plasma. http://web.archive.org/web/20201021220421/https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma

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- 558) 2020-08-23 Gallagher C: Expanded access program for convalescent plasma discontinues enrollment as FDA authorizes its emergency use. Mayo Clinic News Network, August 23, 2020. https://newsnetwork.mayoclinic.org/discussion/expanded-access-program-for-convalescent-plasma-discontinues-enrollment-as-fda-authorizes-its-emergency-use/
- 559) 2020-08-23 Andrus CH: Re: Thousands of Americans are *needless dying* because the FDA is illegally ignoring PL 115-176 The *Right to Try Law*^{1,2} and COVID-19 Convalescent Plasma has NOT been given as Prophylaxis and Early after COVID-19 positivity conversion. Letter mailed to President Trump and the offices of the U.S. Senate. [In the attached CD: 06 Appendices A-H copy/01 Dear Members of Congress and President Trump 8 23 2020]
- 560) 2020-08-24 Thomas K, Fink S: F.D.A. 'Grossly misrepresented' blood plasma data, Scientists say. Many experts—including a scientist who worked on the Mayo Clinic study—were bewildered about where a key statistic came from. *The New York Times*Katiehttps://web.archive.org/web/20200825025014/https://www.nytimes.com/2020/08/24/health/fda-blood-plasma.html
- 561) 2020-08-24 Navarro P: Peter Navarro speaks with reports the day after the EUA announcement regarding COVID-19 Convalescent Plasma. https://www.c-span.org/video/?475057-101/peter-navarro-speaks-reporters

...kinds of successes he has last thing I want to do is talk a little bit about this cot convalescent plasma this is a great thing for the American people cob lesson plasma can reduce the mortality rate by 35 percent 35 percent and. If you see controversy in the news. You should think about this. There should absolutely be no controversy about convalescent plasma this is a therapy that's been used across many diseases for many decades the odds of it. Hurting you are close to 0 the odds of it helping you are close to 100 percent the only issue is how much it can help and according to the f.d.a. a 35 percent reduction in mortality so for me this convalescent plasma debate is in some sense a litmus test if you see anybody on c.n.n. or m s n b c or in the Democratic Party question the f.d.a. decision in any way all they are doing is politicizing this issue and at a cost of American lives we cannot afford in this China virus debate to politicize or therapeutics in convalescent class by me if that's like going after Bambi you know this is the most one of the it's proven safe and effective Thank you all right. I'm a huge. Moment. For. You.

Is late in our judgment where we've been trying to do this for weeks simply with. I'm not I'm not I'm not privy to what the decisions were and what the data there was I haven't looked at that but I can I again I tell you this convalescent plasma is not on controversial it's been used for decades across many diseases. The odds of it hurting you are close to 0 the odds of it helping you are close to 100 percent this is the right to try president this is a time when Americans are dying and this is something that can be useful and so so look this timing issue again I think I think it's a way of people trying to politicize what shouldn't be politicized...

562) 2020-08-25 Dockser Marcus A: Science Behind Convalescent Plasma for Covid-19 is Clouded by Politics in FDA Authorization. The Wall Street Journal Aug 25, 2020.

Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

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https://www.wsj.com/articles/fda-officials-reject-claims-that-convalescent-plasma-decisionwas-politicized-11598362563?mod=article inline

- 563) 2020-08-25 Dulipsingh L, Ibrahim D, Schaefer EJ, Crowell R, Deffenderfer MR, William K, Lima C, McKenzie J, Cook L, Puff J, Onoroski M, Wakefield DB, Eadie RJ, Kleiboeker SB, Nabors P, Hussain SA: SARS-CoV-2 serology and virology trends in donors and recipients of convalescent plasma. Transfus Apher Sci 2020 Aug 25; 59: 1-6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7446657/pdf/main.pdf
- 564) 2020-08-26 Dasgupta A: Is a bradykinin storm brewing in COVID-19? Excess of the inflammatory molecule bradykinin may explain the fluid build-up in the lungs of patients with coronavirus infections. Clinical trials of inhibitors are putting this hypothesis to the test. The Scientist, August 26, 2020. https://www.the-scientist.com/news-opinion/is-a-bradykininstorm-brewing-in-covid-19--67876
- 2020-08-26 Holland S: Dr. Fauci delivers COVID-19 update at joint Grand Rounds. 565) Office of External Affairs, Uniformed Services University, Aug 26, 2020. https://health.mil/News/Articles/2020/08/26/Dr-Fauci-delivers-COVID-19-update-at-joint-Grand-Rounds?page=6#pagingAnchor
- 2020-08-26 HISTORY.COM Editors: Dred Scott Case. https://www.history.com/topics/black-history/dred-scott-case
- 2020-08-28 Hinton D, FDA Chief Scientist: U.S. Food & Drug Administration 567) Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. https://web.archive.org/web/20200829175858/https://www.fda.gov/media/137564/download

Pages 1-2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury (remdesivir)³ for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)4, pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.

On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers has been revised to provide updated clinical trial results and supporting data.⁵ (VERY IMPORTANT: This negative statement: "...by no longer limiting its use to the treatment of patients with severe disease..." is obfuscation by the FDA. The positive statement that the FDA failed to state at the time and FDA has never stated is:

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Veklury (Remdesivir) is indicated most efficaciously in the early treatment of COVID-19 in the viremic phase (best within 72 hours of diagnosis) because it inhibits RNA polymerase replication of the COVID-19 RNA. The justifying REASON for this is: "The active form of remdesivir acts as a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses including SARS-CoV-2. Remdesiviris incorporated by the RdRp into the growing RNA product and allows for addition of three more nucleotides before RNA **synthesis stalls...**" Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, Farnung L, Siewert A, Hobartner C, Cramer P: Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nature Communications (2021)12:279 https://doi.org/10.1038/s41467-020-20542-0 https://www.nature.com/articles/s41467-020-20542-0.pdf

Pages 2-3:

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

Distribution of the authorized Veklury will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA

> Gilead will supply Veklury to authorized distributors⁷, or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;

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¹ U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360 bbb-3. February 4, 2020.

² U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations* Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250

The May 1, 2020 EUA referred to the authorized drug as "remdesivir;" however, Gilead subsequently requested, and FDA concurred, that the Fact Sheets be altered to add references to remdesivir's trade name, "Veklury." "Veklury" is used in this August 28, 2020 reissued letter.

⁴ For purposes of the May 1, 2020 EUA, patients with severe disease were defined as patients with oxygen saturation ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

⁵ Prior to this reissuance and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration

The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider; and

The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

- 2020-08-28 Andrus CH: Re: This is a cover letter to the Congressional Staffer who will 568) initially read the attached packet. After you read this cover letter, please bring it to your Chief of Staff so he or she might assess the importance of showing it to the Congressman or Congresswoman for whom you work. Letter to the Offices of the U.S. House of Representatives. [In the attached CD: 06 Appendices A-H copy/02 Dear Members of the US House of Representatives 8 28 2020]
- 2020-09-01 U.S. Food & Drug Administration: Recommendations for Investigational 569) COVID-19 Convalescent Plasma. https://web.archive.org/web/20200901081726/https://www.fda.gov/vaccines-bloodbiologics/investigational-new-drug-ind-or-device-exemption-ide-processcber/recommendations-investigational-covid-19-convalescent-plasma#Patient%20Eligibility
- 570) 2020-09-02 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. September 2, 2020. https://web.archive.org/web/20201115054330/https://www.fda.gov/vaccines-bloodbiologics/investigational-new-drug-ind-or-device-exemption-ide-processcber/recommendations-investigational-covid-19-convalescent-plasma
- 571) 2020-09-02 U.S. Food & Drug Administration: Investigational COVID-19 Convalescent Plasma – Guidance for Industry. https://web.archive.org/web/20200904181318/https://www.fda.gov/media/136798/download
- 2020-09-02 U.S. Department of Defense: Tricare Coverage of certain medical benefits in 572) response to the COVID-19 pandemic. Regulations.gov. https://www.regulations.gov/document/DOD-2020-HA-0050-0001
- 2020-09-03 Weixel N: White House denies Trump has embraced 'herd immunity' strategy to COVID-19. The Hill. https://thehill.com/policy/healthcare/515025-white-housedenies-trump-has-embraced-herd-immunity-strategy-to-covid

The White House on Thursday again denied the administration has ever considered a policy of "herd immunity" for COVID-19 infections.

"The herd immunity so-called theory was something made up in the fanciful minds of the media. That was never something that was ever considered here at the White House," press secretary Kayleigh McEnany told reporters during a briefing.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals Prevention: Active Immunization: Vaccines

McEnany was responding to reports that new White House pandemic adviser Scott Atlas, a fellow at the conservative Hoover Institution who is not an epidemiologist or infectious diseases expert, had advocated for the Trump administration to lift all restrictions aimed at stopping infections from spreading.

Atlas has publicly downplayed the importance of mask wearing, and has suggested the U.S. shouldn't be testing so many people.

The goal of herd immunity is to get as many "healthy" people infected as possible in order to build widespread resistance, while protecting the most vulnerable populations.

The U.S. has let states take the lead on their own coronavirus strategies, and there has been no centralized response from the White House. The U.S. has recorded more than 6 million COVID-19 infections and more than 186,000 deaths.

White House officials have spent the week denying The Washington Post's report that Atlas has been pushing herd immunity — and that President Trump has been listening.

Trump seemingly referred to herd immunity during an interview with Fox News on Monday.

"Once you get to a certain number, you know — we use the word herd, right?" Trump told Laura Ingraham. "Once you get to a certain number, it's going to go away."

On Wednesday, White House coronavirus task force coordinator Deborah Birx said she would not be a part of the administration if Trump believed herd immunity was a viable strategy.

"Neither I, nor anybody in the administration, is willing to sacrifice American lives for herd immunity. We'll get to herd immunity through a vaccine and that's the right way to do it," Birx said.

Despite the denials, the administration's approach to the pandemic has changed.

- Former deputy national security advisor: 'I think we can' find COVID-...
- Over 100 staff sue Houston Methodist over COVID-19 vaccine requirement
 The Centers for Disease Control and Prevention shifted its guidelines last week, and no longer recommends asymptomatic people get tested even if they have been exposed to someone with the disease.

The strategy serves to underrepresent the true number of people infected with the virus, but lower case numbers could bolster Trump's reelection chances.

Trump and his top aides have also taken to holding public events without wearing a mask and without requiring attendees to wear them, most notably last week's Republican National Convention speech on the White House lawn.

574) 2020-09-04 Root H, Bartelt L, Gilligan P: The promise of COVID-19 Convalescent Plasma Therapy. American Society for Microbiology

https://asm.org/Articles/2020/July/The-Promise-of-COVID-19-Convalescent-Plasma-Therap

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- 575) 2020-09-05 Martines RB, Ritter JM, Matkovic E, Gary J, Bollweg BC, Bullock H, Goldsmith CS, Silva-Flannery L, Seixas JN, Reagan-Steiner S, Uyeki T, Denison A, Bhatnagar J, Shieh W, Zaki SR, and COVID-19 Pathology Working Group: Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. CDC, Centers for Disease Control and Prevention: *Emerging Infectious Diseases*. Sept 2020; 26(9): 2005-2015. Doi: 10.3201/eid26009.202095. https://wwwnc.cdc.gov/eid/article/26/9/20-2095 article
- 576) 2020-09-08 Lowe D: Bradykinin and the coronavirus. https://www.science.org/content/blog-post/bradykinin-and-coronavirus
- 577) 2020-09-15 Simply Wall St: How much does Regeneron Pharmaceuticals' (NASDAQ:REGN) CEO make? https://simplywall.st/stocks/us/pharmaceuticals-biotech/nasdaq-regn/regeneron-pharmaceuticals/news/how-much-does-regeneron-pharmaceuticals-nasdaqregn-ceo-make
- 578) 2020-09-15 Kumar M, Al Khodor S: Pathophysiology and treatment strategies for COVID-19. Journal of Translational Medicine 15 Sept 2020; 18: 353- 361. https://link.springer.com/content/pdf/10.1186/s12967-020-02520-8.pdf
- 579) 2020-09-15 Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, Rodriguez D, Tandon P, Bassily-Marcus A, Bander J, Sanky C, Dupper A, Zheng A, Altman DR, Chen BK, Krammer F, Rao Mendu D, Firpo-Betancourt A, Levin MA, Bagiella E, Casadevall A, Cordon-Cardo C, Jhang JS, Arinsburg SA, Reich DL, Aberg JA, Bouvier NM. Convalescent plasma treatment of severe COVID-19: A matched control study. medRxiv preprint. Published initially on 2020 September 15 as a medRxiv preprint and subsequently Nature Medicine 2020 November; 26: 1708-1713. https://www.nature.com/articles/s41591-020-1088-9.pdf

Abstract Results Convalescent plasma recipients were more likely than control patients to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14, with an odds ratio of 0.86 (95% Cl: 0.75~0.98; p=0.028). Plasma recipients also demonstrated improved survival, compared to control patients (log-rank test: p = 0.039). In a covariates-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19 (95% Cl: 0.05~0.72); p = 0.015), but not for intubated patients (1.24 (0.33~4.67); p = 0.752).

Mr. President: What the abstract results above mean is that if the patients require intubation (at the end of the Cytokine Cascade and Bradykinin Storm), then there was no survival advantage to <u>Passive Immunization</u> with COVID-19 Convalescent Plasma.--<u>BUT</u>, if COVID-19 Convalescent Plasma was given before intubation, in all analyses in this study, there was a significant survival advantage (i.e.: all p values were < 0.05).

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- 580) 2020-09-16 Roth LK: Investigational COVID-19 Convalescent Plasma: Guidance for Industry; Withdrawal of guidance. U.S. Food and Drug Administration, Regulations.gov. Docket (FDA-2020-D-1825). https://www.regulations.gov/document/FDA-2020-D-1825-0011
 - i. FDA is withdrawing the guidance for industry entitled "Investigational COVID-19 Convalescent Plasma" (May 2020 guidance) dated April 2020 and updated May 2020. The availability of this guidance was announced in the Federal Register of May 26, 2020, (85 FR 31513) and was posted on FDA's website on May 1, 2020.
 - ii. On August 23, 2020, the Agency issued an emergency use authorization (EUA) (available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. Given the issuance of this EUA, FDA is issuing a new guidance of the same title that provides recommendations and additional information related to the EUA for the use of COVID-19 convalescent plasma to treat hospitalized patients with COVID-19. The new guidance supersedes the May 2020 guidance. Elsewhere in this issue of the Federal Register, FDA is announcing the availability of the new guidance.
- 581) 2020-09-16 European Blood Alliance: Support-E European project on COVID-19 convalescent plasma. EU Commission allocates 4M grant for SUPPORT-E. https://europeanbloodalliance.eu/activities/convalescent-plasma-cpp/support-e-european-project-on-covid-19-convalescent-plasma/
- 582) 2020-09-19 Altuntas F, Ata N, Yigenoglu TN, Basci S, Dal MS, Korkmaz S, Namdaroglu S, Basturk A, Hacibekiroglu T, Dogu MH, Berber I, Dal K, Kinik D, Haznedaroglu I, Yimaz FM, Kilic I, Demircioglu S, Yosunkaya A, Erkurt MA, Turgut B, Caglayan M, Celik O: Convalescent plasma therapy in patients with COVID-19. Transfusion and Apheresis Science (60) 2021. 102955 Online September 19, 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7501849/pdf/main.pdf
- 583) 2020-09-19 Parshley L: This theory might explain "Covid toes" and other mysteries of the disease. Vox https://www.vox.com/21445038/covid-19-symptoms-treatments-bradykinin-cytokine-storm
- 584) 2020-09-19 Rahaman M, Li Chen, Yao Y, Kulwa F, Rahman MA, Wang Q, Qi S, Kong F, Zhu X, Zhao X: Identification of COVID-19 samples from chest X-ray images using deep learning: A comparison of transfer learning approaches. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7592691/
- 585) 2020-09-20 Ibrahim D, Dulipsingh L, Zapatka L, Eadie R, Crowell R, Williams K, Wakefield DB, Cook L, Puff J, Hussain SA: Factors associationed with good patient

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- outcomes following convalescent plasma in COVID-19: A prospective phase II clinical trial. Infect Dis Ther (2020) 9:913-926. https://europepmc.org/article/med/32983830
- 586) 2020-09-21 U.S. Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2020-D-1825]: Investigational COVID-19 Convalescent Plasma; Guidance for Industry; Availability. Federal Register / Vol. 85, No. 183 / Monday, September 21, 2020 / Notices, 59319 59320. https://www.govinfo.gov/content/pkg/FR-2020-09-21/pdf/2020-20801.pdf
- 587) 2020-09-23 Ward H: Number of annual blood plasma collections in the United States from 2007 to 2019. Statista. https://www.statista.com/statistics/756229/number-of-annual-plasma-collections-in-the-us/
- 588) 2020-09-23 Selvi V: Review Article: Convalescent plasma: A challenging tool to treat COVID-19 patients—A lesson from the past and new perspectives. BioMed Research International. https://downloads.hindawi.com/journals/bmri/2020/2606058.pdf

On March 11th, 2020, the World Health Organization declared COVID-19 infection as a pandemic. Since it is a novel virus, there are basically no proven drugs or therapies; although many laboratories in different countries are working to develop a vaccine, it will take time to make it available. Passive immunization is the therapy born from the intuition of Behring and Kisato in the late 19th century. It was widely used for the treatment of bacterial infections until the discovery of antibiotics, as well as during the viral pandemics of the 20th century and of the beginning of the 21st; it still has clinical applications (e.g., tetanus prevention). This paper summarizes the basic principles of passive immunization, with particular reference to convalescent plasma. The literature concerning its use during past epidemics and the results of the first clinical studies concerning its use during the current pandemic are discussed too. A large section is dedicated to the analysis of the possible, although rare, side effects. Recently, in 2017, the WHO Blood Regulators Network (BRN) published a position paper, recommending convalescent plasma as the first choice treatment to be tested in the absence of authorized drugs; however, this strategy has not been followed. In the current epidemic, the principle of passive immunization through convalescent plasma has been applied in several circumstances and particularly in patients with serious complications. The first reported results are encouraging and confirm the effectiveness of plasma therapy and its safety. Also, the FDA has proposed plasma treatment in order to face the increasingly complex situation and manage patients with serious or immediately life-threatening COVID-19 disease. Several studies and clinical programs are still ongoing.

- **589)** 2020-09-23 Boehmer TK, DeVies J, Caruso E, van Santen KL, Tang S, Black CL, Hartnett KP, Kite-Powel A, Dietz S, Lorzier M, Cundlapalli AV: Changing age distribution of the COVID-19 Pandemic—United States, May-August 2020. Morbidity and Mortality Weekly Report, Centers for Disease Control, U.S. Department of Health and Human Services. https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6939e1-H.pdf
- 590) 2020-09-23 Fara A, Miltrev Z, Rosalia RA, Assas BM: Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. The Royal Society publishing Open Biology. 2020 Sep 23; 10(9): 200160. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7536084/

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- 591) 2020-09-25 Parasher A: COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J 2021;97:312-320. https://pmj.bmj.com/content/postgradmedj/97/1147/312.full.pdf
- 592) 2020-09-25 Pau AK, Aberg J, Baker J, Baker J, Belperio PS, Coopersmith C, Crew P, Grund B, Gulick RM, Harrison C, Kim A, Lane C, Masur H, Sheikh V, Singh K, Yazdany J, Tebas P, for the National Institutes of Health COVID-19 Treatment Guidelines Panel*: Convalescent plasma for the treatment of COVID-19: Perspectives of the National Institutes of Health COVID-19 Treatment Guidelines Panel. Ann of Internal Med 2021 Jan; 174 (1): 93-95. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7556653/pdf/aim-olf-M206448.pdf
 This article was published at Annals.org on 25 September 2020, * For members of the National Institutes of Health COVID-19 Treatment Guidelines Panel, see the Appendix Table (available at Annals.org). [This is such an important article that it has been copied and pasted to follow in its entirety. This is the NIH's justification of merging Phase I (safety) trials with Phase II (efficacy) trials so as to circumvent completely ever applying PL-115-176: The Right to Try Law with regards to COVID-19 Convalescent Plasma but also any future investigational drug or biologic ad infinatum. This obfuscation by the NIH is tantamount to justifying repeated violations of PL-115-176 and is ethically shameful!].

Currently, no Food and Drug Administration (FDA)—approved therapeutics exist for coronavirus disease 2019 (COVID-19). In this context, the pandemic has put considerable pressure on health care providers to prescribe treatments despite limited information about their safety and efficacy. This pressure has exacerbated the tension between the importance of practicing evidence-based medicine and the urgency of providing access to promising therapies before their safety and efficacy are established.

A strong scientific rationale and historical precedents exist for the study of passive immunotherapeutic approaches for viral infections (4). Concentrated, virus-specific immunoglobulin preparations are FDA approved for the postexposure prophylaxis of such viral infections as hepatitis B, varicella, and rabies (5). Recently, a randomized controlled trial (RCT) demonstrated the efficacy of 2 different monoclonal antibody products for treating Ebola virus disease (6).

On 23 August 2020, the FDA issued an Emergency Use Authorization (EUA) for convalescent plasma for treating COVID-19 (2). An EUA does not constitute drug approval by the FDA. Rather, an EUA allows the FDA to facilitate the availability and unapproved uses of medical products during a public health emergency (3). The criteria for issuing an EUA for medical products include the following: The public health concern must be serious or life threatening; sufficient evidence must exist that the product "may be effective"; the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product; and no adequate, approved alternatives to the product are available (3).

A strong scientific rationale and historical precedents exist for the study of passive immunotherapeutic approaches for viral infections (4). Concentrated, virus-specific immunoglobulin preparations are FDA approved for the postexposure prophylaxis of such viral infections as hepatitis B, varicella, and rabies (5). Recently, a randomized controlled trial (RCT)

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demonstrated the efficacy of 2 different monoclonal antibody products for treating Ebola virus disease (6).

The situation is less clear regarding the safety and efficacy of convalescent plasma, which has been used to treat viral infections from the 1918 influenza pandemic to the recent epidemics of severe acute respiratory syndrome (SARS), H1N1 influenza, Middle East respiratory syndrome. and Ebola virus disease (7-10). The only RCT demonstrating efficacy of convalescent plasma for an infectious disease was conducted more than 40 years ago, for treating Argentine hemorrhagic fever (11).

Early in the COVID-19 pandemic, convalescent plasma was used in China to treat hospitalized patients with COVID-19 (7). Shortly thereafter, RCTs evaluating convalescent plasma in patients with COVID-19 began in several countries, including the United States (12). In March 2020, the FDA authorized expanded access to convalescent plasma for treating severe or life-threatening COVID-19 under individual-patient emergency Investigational New Drug applications. The Mayo Clinic's Expanded Access Program (EAP) was developed in parallel to provide broader access to convalescent plasma; however, it was not designed to generate definitive data on safety or to evaluate efficacy (13). One of the requirements for an EAP is that it not interfere with pivotal trials (14). Adequately powered RCTs of convalescent plasma in the United States have been slow to enroll patients.

Given the lack of data from properly powered RCTs, and the need to inform regulatory decision making regarding continued access to convalescent plasma, both the FDA and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using EAP data, hypothesizing that patients who received plasma units with higher titers of neutralizing antibodies would have better clinical outcomes. The results of the analyses were used as supporting evidence for the EUA.

The FDA analysis included 4330 patients, and donor neutralizing antibody titers were measured by the Broad Institute, using a SARS coronavirus 2 (SARS-CoV-2) neutralization assay (15). The analysis revealed no difference in 7-day mortality between the patients who received high-titer and those who received low-titer plasma in the overall population or in the subset of patients who were intubated. However, among nonintubated patients (approximately two thirds of those analyzed), 11% of those who received high-titer plasma died within 7 days of transfusion compared with 14% who received low-titer plasma (P = 0.03) (16). In a post hoc analysis of nonintubated patients who were younger than 80 years and treated within 72 hours of diagnosis, 7-day mortality for those who received high- versus low-titer plasma was 6.3% and 11.3%, respectively (P = 0.0008)

A similar efficacy analysis by the Mayo Clinic included 3082 participants who had received a single unit of plasma among the 35 322 participants who had received plasma through the EAP by 4 July 2020 (17). Antibody titers were measured by using the VITROS anti–SARS-CoV-2 IgG assay (Ortho Clinical Diagnostics), and outcomes were compared among patients receiving low-(lowest 18%), medium-, and high-titer (highest 17%) plasma. After adjusting for baseline characteristics, the 30-day mortality rate was 29.1% in the low-titer group and 24.7% in the hightiter group. This difference did not reach statistical significance. The Mayo Clinic post hoc subgroup analyses also suggested a benefit of high-titer plasma in patients who received plasma within 3 days of COVID-19 diagnosis (17).

The FDA concluded that the totality of data, including additional data from small randomized trials and nonrandomized, observational, and animal studies, met the criteria for EUA issuance.

Despite clearly meeting the "may be effective" criterion for EUA issuance, the analyses of the EAP data are not sufficient to establish the efficacy or safety of convalescent plasma because of the lack of an untreated control group. For example, the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded. In addition, the EAP data may be subject to several confounders, including regional

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----- May 30, 2022 -----

differences and temporal trends in COVID-19 management. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers in convalescent plasma from patients who have recovered from COVID-19 are highly variable. In addition, the analyses focused on early mortality, which may not be clinically meaningful in the context of the prolonged disease course of COVID-19. The efficacy analyses rely on a subset of EAP patients and thus represent only a fraction of patients who received plasma through the EAP (17). In this regard, additional analyses of the EAP cohort and completion of the current RCTs will be of critical importance.

Taking everything into account, the Panel has determined that currently the data are insufficient to recommend for or against convalescent plasma for treating COVID-19 (18). Prospective, well-controlled, and adequately powered RCTs are needed to determine whether convalescent plasma and other passive immunotherapies are effective and safe for COVID-19 treatment. Although providers have access to this therapy, the Panel cannot recommend it as a standard of care for treating COVID-19 at this time. This is consistent with the language of the convalescent plasma EUA Fact Sheet (19).

The COVID-19 pandemic has intensified the tension between providing rapid access to promising therapies and generating the scientific evidence needed to establish whether those therapies are safe and effective. This tension was also noted during the West African Ebola outbreak in 2014 to 2016, when several therapies, including convalescent plasma, were claimed to be of benefit. A National Academies of Sciences, Engineering, and Medicine review of that response noted that RCTs are critical during an outbreak, because they are the quickest way to identify effective therapies (20). Experience with convalescent plasma, hydroxychloroquine, and other interventions has taught us that large observational cohorts, EAPs, and EUAs can have a profound impact on our ability to conduct the properly designed RCTs necessary to provide definitive evidence of safety and efficacy. Conversely, the lack of access to large RCTs at many health care centers during the COVID-19 pandemic may exacerbate issues of equity in access to care. Expanded Access Programs continue to be an important mechanism to provide promising therapies for patients who do not otherwise have access to them (that is, through clinical trials). Balancing this tension is challenging but imperative to maintaining the ability to generate rigorous and convincing evidence during a public health crisis.

Despite the challenges of the COVID-19 pandemic, conducting well-controlled, adequately powered RCTs is possible. Two such trials, ACTT (Adaptive COVID-19 Treatment Trial) and RECOVERY (Randomized Evaluation of COVID-19 Therapy), recently demonstrated the efficacy of remdesivir and dexamethasone, respectively, for treating COVID-19 (21, 22). Collaboration and partnership among governmental agencies, industry, academia, and the public are needed to establish and carry out a robust and coordinated emergency research response, including the rapid development, deployment, and analysis of high-caliber RCTs. This approach is the quickest and most efficient way to generate the answers needed to provide the best evidence-based patient care.

- 593) 2020-09-26 St. Louis Regional Health Commission: History—1970s to 2000s Hospital closures threaten health care safety net. https://www.stlrhc.org/who-we-are/history/
- 594) 2020-09-29 Regeneron: Regeneron's REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients. While this detailed report by Regeneron to its investors was mentioned in the *Roche Investor Update* of 2020-09-30 https://www.roche.com/investors/updates/inv-update-2020-09-30.htm the URL of this report https://investor.regeneron.com/news-

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releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and but can be found in its entirety using the Internet Archive (Wayback Machine)
http://web.archive.org/web/20201030083248/https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and This series of articles have legitimated de facto withholding of the early administration (<72 hours) of Passive Immunization to every American who tested positive going forward. Please note that the following news reports confirmed the existence of the original document:

Carlson R: COVID-19 antibody cocktail found very effective. Precision Vaccinations, September 30, 2020.

https://www.precisionvaccinations.com/covid-19-antibody-cocktail-found-very-effective

Beasley D: Regeneron says its COVID-19 treatment reduces viral levels, improves symptoms. Reuters APAC September 29, 2020, 9:16 PM. https://www.reuters.com/article/health-coronavirus-treatment-reduces-viral-levels-improves-symptoms-idUSKBN26L08A

CNBC: Regeneron says its coronavirus treatment reduces viral levels, improves symptoms. Published Tue, Sep 29 2020, 4:19; Updated Tue, Sep 29, 2020, 4:41 PM. https://www.cnbc.com/2020/09/29/regeneron-says-its-covid-19-treatment-reduces-viral-levels-improves-symptoms.html

World Pharma Today: Regeneron's REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients. https://www.worldpharmatoday.com/news/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and-improved-symptoms-in-non-hospitalized-covid-19-patients-2/. The hyperlink contained within this site contains the *verbatim* copy of the missing Regeneron announcement that was accessed by the Wayback Machine above. https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and; attached to this is another URL that summarized the outcomes: https://c19regn.com/regeneron.html with the graphic interpretation recorded as 5/12/2021(today) of the outcomes: https://c19regn.com/r

September 29, 2020 at 4:01 PM EDT

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REGENERON'S REGN-COV2 ANTIBODY COCKTAIL REDUCED VIRAL LEVELS AND IMPROVED SYMPTOMS IN NON-HOSPITALIZED COVID-19 PATIENTS

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

TARRYTOWN, N.Y., Sept. 29, 2020 /PRNewswire/ --

Greatest improvements in patients who had not mounted their own effective immune response prior to treatment

Plan rapidly to discuss results with regulatory authorities

Regeneron to host investor and media webcast to discuss results at 4:30 pm ET today

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced the first data from a descriptive analysis of a seamless Phase 1/2/3 trial of its investigational antibody cocktail REGN-COV2 showing it reduced viral load and the time to alleviate symptoms in non-hospitalized patients with COVID-19. REGN-COV2 also showed positive trends in reducing medical visits. The ongoing, randomized, double-blind trial measures the effect of adding REGN-COV2 to usual standard-of-care, compared to adding placebo to standard-of-care.

This trial is part of a larger program that also includes studies of REGN-COV2 for the treatment of hospitalized patients, and for prevention of infection in people who have been exposed to COVID-19 patients.

"After months of incredibly hard work by our talented team, we are extremely gratified to see that Regeneron's antibody cocktail REGN-COV2 rapidly reduced viral load and associated symptoms in infected COVID-19 patients," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "The greatest treatment benefit was in patients who had not mounted their own effective immune response, suggesting that REGN-COV2 could provide a therapeutic substitute for the naturally-occurring immune response. These patients were less likely to clear the virus on their own, and were at greater risk for prolonged symptoms. We are highly encouraged by the robust and consistent nature of these initial data, as well as the emerging well-tolerated safety profile, and we have begun discussing our findings with regulatory authorities while continuing our ongoing trials. In addition to having positive implications for REGN-COV2 trials and those of other antibody therapies, these data also support the promise of vaccines targeting the SARS-CoV-2 spike protein."

The descriptive analysis included the first 275 patients enrolled in the trial and was designed to evaluate anti-viral activity with REGN-COV2 and identify patients most likely to benefit from treatment; the next cohort, which could be used to rapidly and prospectively confirm these results, has already been enrolled. Patients in the trial were randomized 1:1:1 to receive a one-time infusion of 8 grams of REGN-COV2 (high dose), 2.4 grams of REGN-COV2 (low dose) or placebo. All patients entering the trial had laboratory-confirmed COVID-19 that was being treated in the outpatient setting. Patients were prospectively characterized prior to treatment by serology tests to see if they had already generated antiviral antibodies on their own and were classified as seronegative (no measurable antiviral antibodies) or seropositive (measurable antiviral antibodies). Approximately 45% of patients were seropositive, 41% were seronegative and 14% were categorized as "other" due to unclear or unknown serology status.

595) 2020-09-30 Johnson CY: These laboratory-made antibodies are a best bet for a coronavirus treatment, but there won't be enough. The Washington Post https://www.washingtonpost.com/health/2020/09/30/monoclonal-antibodies-to-treat-covid-19/

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- 596) 2020-10 Behrns KE, Wexner SD: Times are changing and so is *Surgery*. Drs. Behrns and Wexner are the editors-in-chief. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489221/
- 597) 2020-10 Abasaeed Elhag S, Ibrahim H, Abdelhadi S: Angioedema and urticaria in a COVID-19 patient: A case report and review of the literature. JAAD Case Reports 2020 October; 6(10): 1091-1094.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7403866/pdf/main.pdf

A plausible explanation for the development of angioedema lies in the established **correlation between SARS-CoV-2 and** angiotensin-converting exzyme **2**, **a receptor** for the virus to enter the epithelial cells of the lungs. It is known that angiotensin-converting enzyme-2 has a crucial role in the inhibition of des-ARG9 bradykinin, which is a potent ligand of bradykinin receptor 1. Hence, the inhibition of angiotensin-converting enzyme 2 has a crucial role in the inhibition of angiotensin-converting enzyme 2 leads to excessive activation of the bradykinin pathway, and subsequently increases vascular permeability leading to angioedema. This is similar to the proposed mechanism by which this virus causes acute pulmonary edema and acute respiratory distress.

- 598) 2020-10 Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, Xia X, Lv T: Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Me Virol. 2020; 92: 1890-1901. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25882
- 599) 2020-10-01 Hinton D, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. http://web.archive.org/web/20201015193426/https://www.fda.gov/media/137564/download
- 600) 2020-10-01 Farag YMK: Letter to the Editor: Limitations of safety update on convalescent plasma transfusion in COVID-19 patients. Mayo Clin Proc 2020 Dec; 95(12): 2801-2802. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7528833/pdf/main.pdf
- 601) 2020-10-01 Joyner MJ, Senefeld JW, Klassen SA, Fairweather D, Wright RS: In Reply Limitations of safety update on convalescent plasma transfusion in COVID-19 patients. Mayo Clinic Proc 2020 Dec; 95 (12): 2801-2803. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7528832/pdf/main.pdf
- 602) 2020-10-02 Homer M: Timeline: What we know about Regeneron's antibody cocktail that was given to President Trump.

 https://www.khou.com/article/news/health/coronavirus/trump-regeneron-polyclonal-antibody-cocktail/285-636b1f14-fed2-42f3-8b41-0a565a2dd967

They are "a real best chance of being a game changer," NIH Director Francis S. Collins told the Washington Post about the experimental drug.

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- 2020-10-05 Philippidis A, LeMieux J: Trump's treatments: Regeneron's antibodies and Gilead's Remdesivir explained. Genetic Engineering & Biotechnology News. https://www.genengnews.com/insights/trumps-treatments-regenerons-antibodies-and-gileadsremdesivir-explained/
- 2020-10-05 LaMonica PR: Trump has ties to drugmaker Regeneron and now its stock is surging. CNN Business https://www.cnn.com/2020/10/05/investing/trumpregeneron/index.html

New York (CNN Business)President Trump received a high dose of an experimental antibody cocktail from Regeneron as part of his Covid-19 treatment. Now the drugmaker's stock is up sharply -- and questions are swirling about the president's ties to Regeneron's billionaire CEO.

Trump's team revealed Friday that the president received the drug, called REGN-COV2, which is being used to alleviate symptoms and reduce viral load. Shares of Regeneron surged 7% Monday, bringing the stock's year-to-date gain to more than 60%. The stock reached its highs of the day after Trump tweeted that he will be leaving the hospital Monday evening.

Regeneron CEO Dr. Leonard Schleifer and President Trump are acquainted: The CEO has been a member at Trump's golf club in Westchester, New York, and his company also received \$450 million in government funding in July as part of the president's Operation Warp Speed plan to quickly develop a vaccine and other treatments for Covid-19.

Meanwhile, Trump also recently owned shares of Regeneron (REGN) -- as well as Gilead Sciences (GILD), maker of the antiviral drug remdesivir that the president is also taking. Both stocks were listed as assets on Trump's 2017 filing with the U.S. Office of Government Ethics, though neither were holdings on the president's most recent filing for 2020.

"Len and President Trump are acquaintances from both living in the Westchester area for many years but didn't have any regular contact until this year, when they've discussed matters around Covid on occasion," Regeneron told CNN Business in a statement.

According to Forbes, Schleifer is now worth \$2.5 billion, up from \$2.1 billion in the middle of March. Schleifer primarily donated to Democratic political candidates and PACs in the 2016 and 2018 elections, according to Federal Election Commission records.

Regeneron is one of many biotechs and Big Pharma firms that has skyrocketed on hopes that it may be able to quickly develop an effective coronavirus treatment. The company started human trials for its antibody cocktail in June and began a phase 3 trial just a month later.

It has not yet been approved by the Food and Drug Administration, however. The FDA can approve the administration of it through so-called compassionate use requests on an individual basis. Regeneron confirmed to CNN Business that one of the president's doctors made such a request to Regeneron and the FDA to approve administering the drug to Trump.

Schleifer defended the decision to give Trump the cocktail last week, telling CNN's Wolf Blitzer that Trump "is in a higher-risk group for a variety of reasons" and that "we hope that we will give his immune system enough of a boost so that he can win this and make a complete recovery." "We've got a lot of data, but we're still in the experimental phase. But when you're in the midst of a pandemic and you have people at risk, we think it makes sense to try these," Schleifer added. Regeneron added in its statement to CNN Business that it is "in discussions with the FDA about potential for an Emergency Use Authorization for REGN-COV2" following the release of positive data about the drug last week.

The company had announced just a few days before President Trump's admission to Walter Reed that its cocktail "reduced viral load and the time to alleviate symptoms in non-hospitalized patients."

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Regeneron said it is also in the process of studying the effect of the cocktail on hospitalized patients, as well as whether it can prevent infection in people who have been exposed to Covid-19. Dr. George Yancopoulos, Regeneron's president and chief scientific officer, told CNN's Julia Chatterley in an interview Monday that the company is hoping it can get more doses of REGN-COV2 to patients within the next few months thanks to a partnership with Big Pharma giant Roche.

"We are on track to deliver 300,000 doses by the end of the year and...produce 300,000 doses a month while the demand may even still exceed that," Yancopoulos said. "If the drug is really working and having the effects that we all hope it would, it could be doing a lot of good for a lot of people."

Correction: An earlier version of this story misstated the compassionate use request process. One of the president's physicians made the request to Regeneron and the FDA.

- 605) 2020-10-05 Cohen J: Update: Here's what is known about Trump's COVID-19 treatment. Science https://www.sciencemag.org/news/2020/10/heres-what-known-about-president-donald-trump-s-covid-19-treatment
- 606) 2020-10-05 Gringlas S, Sprunt B: Timeline: What we know of President trump's COVID-19 diagnosis, treatment. NPR. https://www.npr.org/sections/latest-updates-trump-covid-19-results/2020/10/03/919898777/timeline-what-we-know-of-president-trumps-covid-19-diagnosis
- 607) 2020-10-05 Wilt TJ, Kaka AS, MacDonald R, Greer N, Obley A, Duan-Porter: Remdesivir for Adults with COVID-19—A living systematic review for an American College of Physicians Practice Points. Ann Internal Med, Published at Annals.org on 5 October 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7564604/pdf/aim-olf-M205752.pdf

[Mr. President, the VA <u>DID NOT EVEN READ its own publications</u>! One month after this publication (the abstract is pasted below) and after Velkury (remdesivir) was approved by the FDA on October 22, 2020 as the only licensed drug to this day in the treatment of COVID-19: NDA #21478, the VA Central Office issued Remdesivir (VELKURY) Criteria for Use, November 2020 limiting use of Velkury (remdesivir) to only: "Inclusion Criteria, The following must be fulfilled in order to meet the criteria for remdesivir: Hospitalized with SEVERE COVID-19 [room air oxygen saturation <94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO[***"] In December e-mail discussions (see Appendices E of this correspondence) with Richard Stone, M.D., former VHA Chief Medical Executive (former Acting VHA Undersecretary for Health during the early part of your administration), I pointed out this Significant Directive Error to Dr. Stone as well as the FDA, the NIH, and the Editors of The New England Journal of Medicine. THIS INCORRECT DIRECTIVE of VA policy CONTINUES EVEN TO THIS DAY, AUGUST 5, 2021, and is ACCESSIBLE ON THE INTERNET as VA policy. Also, please note the FDA removed the erroneous administration criteria from all its publications on August 28, 2020 and RADM Hinton, FDA Chief Scientist, encouraged early administration of remdesivir (COVID-19 viremic phase) in the individual patient after COVID-19 laboratory confirmation in the asymptomatic state and forward.

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Annals of Internal Medicine

REVIEW

Remdesivir for Adults With COVID-19

A Living Systematic Review for an American College of Physicians Practice Points

Timothy J. Wilt, MD, MPH; Anjum S. Kaka, MD; Roderick MacDonald, MS; Nancy Greer, PhD; Adam Obley, MD; and Wei Duan-Porter, MD, PhD

Background: Few treatments exist for coronavirus disease 2019 (COVID-19).

Purpose: To evaluate the effectiveness and harms of remdesivir for COVID-19.

Data Sources: Several databases, tables of contents of journals, and U.S. Food and Drug Administration and company websites were searched from 1 January through 31 August 2020.

Study Selection: English-language, randomized trials of remdesivir treatments for adults with suspected or confirmed COVID-19. New evidence will be incorporated using living review methods.

Data Extraction: Single-reviewer abstraction and risk-of-bias assessment verified by a second reviewer; GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods used for certainty-of-evidence assessments.

Data Synthesis: Four randomized trials were included. In adults with severe COVID-19, remdesivir compared with placebo probably improves recovery by a large amount (absolute risk difference [ARD] range, 7% to 10%) and may result in a small reduction in mortality (ARD range, -4% to 1%) and a shorter time to recovery or clinical improvement. Remdesivir may have little to no effect on hospital length of stay. Remdesivir probably reduces serious adverse events by a moderate amount (ARD range, -6% to -8%). Compared with a 10-day remdesivir course, a 5-day

course may reduce mortality, increase recovery or clinical improvement by small to moderate amounts, reduce time to recovery, and reduce serious adverse events among hospitalized patients not requiring mechanical ventilation. Recovery due to remdesivir may not vary by age, sex, symptom duration, or disease severity.

Limitations: Low-certainty evidence with few published trials, including 1 preliminary report and 2 open-label trials. Trials excluded pregnant women and adults with severe kidney or liver disease.

Conclusion: In hospitalized adults with COVID-19, remdesivir probably improves recovery and reduces serious adverse events and may reduce mortality and time to clinical improvement. For adults not receiving mechanical ventilation or extracorporeal membrane oxygenation, a 5-day course of remdesivir may provide similar benefits to and fewer harms than a 10-day course.

Primary Funding Source: U.S. Department of Veterans Affairs, Veterans Health Administration Office of Research and Development, Health Services Research and Development Service, and Evidence Synthesis Program.

Ann Intern Med. doi:10.7326/M20-5752

For author, article, and disclosure information, see end of text.

This article was published at Annals.org on 5 October 2020.

Annals.org

Inclusion Criteria

The following must be fulfilled in order to meet criteria for remdesivir

- Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
- 608) 2020-10-05 McKenzie H: Could an intranasal COVID-19 vaccine be more efficient and effective than traditional approach? https://www.biospace.com/article/why-an-intranasal-covid-19-vaccine-could-be-more-efficient-and-effective/
- 609) 2020-10-06 Rogers TN: Meet the billionaire doctors behind Regeneron, the pharmaceutical company that developed Trump's experimental COVID-19 treatment. https://www.businessinsider.com/regeneron-billionaires-schleifer-yancopoulos-trump-covid-drug-2020-10
- 610) 2020-10-06 Jennings DG: Is Regeneron (NASDAQ: REGN) making money?—Market Mad House. https://marketmadhouse.com/is-regeneron-nasdaq-regn-making-money/

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611) 2020-10-07 Loftus P: Eli Lilly asks FDA to authorize Covid-19 antibody Drug. Wall Street Journal, Updated October 7, 2020, 11:31 pm ET. https://www.wsj.com/articles/eli-lilly-asks-fda-to-authorize-covid-19-antibody-drug-11602074998

If cleared for use, the drug could be the first to treat less severe cases of Covid-19. The few other therapies authorized for Covid-19 treatment, including remdesivir from <u>Gilead Sciences</u> Inc. GILD 1.41% and <u>convalescent plasma</u>, target hospitalized patients with more serious cases.

Lilly said it would seek authorization for use in higher-risk patients to prevent their recently diagnosed mild-to-moderate disease from worsening to a severe state. Executives of the Indianapolis-based company said higher-risk groups may include people 65 years of age or older or obese patients.

"Anything that helps with preventing hospitalization and preventing progression is going to be a big advance," Rajesh Tim Gandhi, an infectious-disease physician at Massachusetts General Hospital and Harvard Medical School, said in an interview.

Lilly's antibody drug could also be the first in a new class of Covid-19 agents that not only might provide treatment but also potentially give temporary protection against the virus to people at risk of infection. That would <u>fill a gap until vaccines are authorized</u>, though people may need to take the antibody drugs more than once to sustain the protection.

"When we started this project we always believed that vaccines would be a long-term solution but that antibodies could come to patients faster," Lilly research head Daniel Skovronsky said in an interview. "We can make them faster, test them faster."

The leading experimental antibody drugs have shown enough promise in testing so far that President Trump was given one developed by Regeneron Pharmaceuticals Inc. Regeneron said Wednesday night it has asked the Food and Drug Administration to authorize use of its antibody drug cocktail for Covid-19. The company said it has supply for 50,000 patients available and will have 300,000 within a few months.

Lilly said last month its drug reduced the rate of hospitalization compared with a placebo in a study. About 1.6% were hospitalized or visited the emergency room for Covid-19 after being injected with the drug, compared with 5.8% of people who didn't get the drug in the study

- antibody treatment. CNN Health. The 3 minute 42 second video attached to this article is the most succinct overview of antibody therapies that should be employed in the treatment of COVID-19 regarding both **Passive Immunization** [the early administration of exogenous neutralizing antibodies to individuals (<72 hours of COVID-19 detection or prophylactically)] and **Active Immunization** [vaccination of an individual which is prevention after the ~ 2-3 week increasing development of neutralizing antibodies in the uninfected individual). https://www.cnn.com/2020/10/07/health/eli-lilly-antibody-therapy-results-eua/index.html
- 613) 2020-10-08 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil A, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

DC, Ohmagari N, Oh Myoung-don, Ruiz-Palacios GM, Benfield T, Fatkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Bergess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC, for the ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 – Final Report. NEJM.org, October 8, 2020. Published in harcopy N Engl J Med 2020; 383:1813-1826. November 5, 2020. A preliminary version of this article was published on May 22, 2020. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764.

SAFETY OUTCOMES

In the as-treated population, serious adverse events occurred in 131 of 532 patients (24.6%) in the remdesivir group and in 163 of 516 patients (31.6%) in the placebo group (Table S17). There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients) (Table S19). No deaths were considered by the investigators to be related to treatment assignment.

Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group (Table S18); 41 events were judged by the investigators to be related to remdesivir and 47 events to placebo (Table S17). The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, and increased blood glucose level (Table S20). The incidence of these adverse events was generally similar in the remdesivir and placebo groups.

Given the preliminary results about remdesivir, the Food and Drug Administration issued an Emergency Use Authorization on May 1, 2020 (modified on August 28, 2020), to permit the use of remdesivir for treatment in adults and children hospitalized with suspected or laboratory-confirmed Covid-19. Remdesivir has also received full or conditional approval in several other countries since that time. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients. Current strategies are evaluating remdesivir in combination with modifiers of the immune response (e.g., the Janus kinase [JAK] inhibitor baricitinib in ACTT-2, and interferon beta-1a in ACTT-3). A variety of therapeutic approaches including novel antivirals, modifiers of the immune response or other intrinsic pathways, and combination approaches are needed to continue to improve outcomes in patients with Covid-19.

- 614) 2020-10-08 Beaumont P, Boseley S, Glenza J: Provider of Trump Covid drug is president's golf friend. https://www.theguardian.com/world/2020/oct/08/provider-of-trump-covid-drug-is-presidents-golf-friend
- 615) 2020-10-08 Hart R: While Trump touts 'Cure' made by Regeneron, Its CEO is a member of Trump golf club. October 8, 2020.

https://www.forbes.com/sites/roberthart/2020/10/08/while-trump-touts-cure-made-by-regeneron-its-ceo-is-a-member-of-trump-golf-club/?sh=22fa6b7a60c8

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals **Prevention**: Active Immunization: Vaccines

616) 2020-10-09 NIH—COVID-19 Treatment Guidelines – Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, Convalescent Plasma. Last Updated: October 9,2020, Page 102-108.

https://files.covid19treatmentguidelines.nih.gov/guidelines/archive/covid19treatmentguidelines-10-09-2020.pdf

Convalescent Plasma

Last Updated: October 9, 2020

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.¹

Recommendation

 There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance.^{2,3} Despite meeting the "may be effective" criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population.^{4,5} Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing.

The Panel's assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents. 3.6.7

- 617) 2020-10-09 Hancock J: As Trump touts his 'great' COVID drugs, the pharma cash flows to Biden, not him. https://khn.org/news/trump-touts-covid-cure-regeneron-drug-pharma-political-contributions-strongly-benefit-biden/
- 618) 2020-10-10 BBC: White House hosted Covid 'superspreader' event, says Dr Fauci. https://www.bbc.com/news/election-us-2020-54487154

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- 619) 2020-10-10 Zimmermann P, Curtis N: Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Arch Dis Children 2020;0:1-11. https://adc.bmj.com/content/archdischild/early/2020/11/30/archdischild-2020-320338.full.pdf
- 2020-10-11 Mack E: Regeneron CEO, a Dem Donor, rejects his treatment as 'Cure'. Newsmax https://www.newsmax.com/politics/regeneron-cure-treatmentcovid/2020/10/11/id/991436/
- 621) 2020-10-11 O'Brien C: Regeneron CEO: Trump 'is a case of one' and 'weakness evidence' for Covid-19 treatment. Politico https://www.politico.com/news/2020/10/11/regeneron-trump-covid-coronavirus-428691
- 622) 2020-10-11 Smith A: Trump declares himself 'immune' to Covid-19. His doctors won't say when he last tested negative. NBC News. https://www.nbcnews.com/politics/2020election/trump-declares-himself-immune-covid-19-his-doctors-won-t-n1242851
- 623) 2020-10-12 Tillett R, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, Laverdure C, Verma SC, Rossetto CC, Jackson D, Farrell MJ, van Hooser S, Pandori M: Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Infect Dis 2020; 21: 52-58. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550103/pdf/main.pdf
- 624) 2020-10-14 Eli Lilly and Company: Lilly statement on the NIAID decision to pause enrollment in ACTIV-3 clinical trial. https://www.lilly.com/news/stories/statement-activ3clinical-trial-covid19-niaid-decision-pause-enrollment
- 625) 2020-10-14 Volkman E: Eli Lilly coronavirus antibody drug trial paused—The National Institutes of Health put the brakes on the study in what the drugmaker calls "an abundance of cautions." The Motley Fool https://www.fool.com/investing/2020/10/14/eli-lillycoronavirus-antibody-drug-trial-paused/
- 2020-10-14 Buchanan L, Gamio L, Leatherby L, Keefe J, Koetti C, Schoenfeld Walker A: Tracking the White House Coronavirus Outbreak. The New York Times https://www.nytimes.com/interactive/2020/10/02/us/politics/trump-contact-tracingcovid.html
- 2020-10-16 Hinton D, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. https://web.archive.org/web/20201017135559/https://www.fda.gov/media/137564/download

Pages 1-2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury (remdesivir)³ for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)⁴, pursuant to Section 564 of the Act.

----- May 30, 2022 -----This is a COVID-19 Timeline Bibliography for Educational Purposes <u>ONLY</u> in the presentation of this information before the people of the United States of America (U.S.A.), the World, and president and president and the Desident and the Country of the United States of America (U.S.A.), the World and president and president and the Country of the United States of America (U.S.A.), the World and president and the Country of the United States of the of America (U.S.A.), the World, and specifically the President of the U.S.A. without any compensation to the author. All submissions including this timeline bibliography can be obtained under the Freedom of Information Act (FOIA) by formally requesting a copy of NIAID Case #12276 from the FIOA Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

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Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.

On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the May 1, 2020, letter in its entirety with revisions incorporated to **expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease.** In addition, the Fact Sheet for Health Care Providers was revised to provide updated clinical trial results and supporting data.⁵

CONTRARY TO REFERENCE #4 WHICH STATES: "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).", AS OF AUGUST 28, 2020, ... "expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."

On October 1, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the August 28, 2020, letter in its entirety with revisions incorporated to the scope and conditions of authorization designating Gilead Sciences, Inc. and its authorized distributors⁶ as the responsible parties for the distribution⁷ of Velkury. FDA is reissuing the October 1, 2020, letter in its entirety with revisions to clarify that an alternate care site (ACS) meeting certain criteria is considered an "inpatient hospital setting" for the purposes of the scope of the EUA, and as such, is within the terms and conditions of FDA's authorization.

Veklury has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), it is reasonable to believe that Veklury may be effective and the known and potential benefits of Veklury outweigh the known and potential risks of the drug for the treatment of patients hospitalized with COVID-19.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Veklury for treatment of COVID-19, as described in the Scope of Authorization section of this reissued letter (Section II) and subject to the terms of this authorization.

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¹ U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

² U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).*

³ The May 1, 2020, EUA referred to the authorized drug as "remdesivir;" however, Gilead subsequently requested, and FDA concurred, that the Fact Sheets be altered to addreferences to remdesivir's trade name, "Veklury." "Veklury" is used in the August 28, 2020, reissued letter.

⁴ For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). (PLEASE NOTE THAT AFTER AUGUST 28, 2020 THESE "SEVERITY OF DISEASE" WERE REVOKED BY THE FDA.)

dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance); (3) added hypersensitivity reaction and drug interaction information; (4) added safety information from randomized ,clinical trials; (5) removed information related to the compassionate use program; and (6) added reference to remdesivir's trade name, Veklury.

Page 3:

3. There is no adequate, approved, and available alternative to the emergency use of Veklury for the treatment of COVID-19. 8

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an inpatient hospital setting⁹ via intravenous (IV) infusion by a healthcare provider; and
- The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

628) 2020-10-19 BBC News: England boosting plasma stocks for patients.

https://www.bbc.com/news/health-54597690

NHS Blood and Transplant is boosting stocks of blood plasma for very ill coronavirus patients ahead of winter.

It wants more people who have recovered from Covid-19 to become donors.

Their plasma contains antibodies that are believed to help other sufferers fight the virus.

Fourteen new donation centres will open in November and December, to bring the total in England to 42. The blood plasma will be used to treat patients in Covid trials.

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⁵ Prior to the reissuance of the EUA on August 28, 2020, and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified

⁶ "Authorized Distributor(s)" are identified by Gilead as an entity or entities allowed to distribute authorized Veklury.

⁷ Allocations of Veklury directed by the United States Government on or before September 30, 2020, remain valid and shall be distributed in collaboration with state or local government authorities, as needed.

⁸ No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

⁹ Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.

capacity and capability for communities overwhelmed by patients with COVID-19.

The product labeled "investigational use" is authorized for use under this EUA; FDA is not requiring it to be relabeled given the immediate need for the product.

- 629) 2020-10-20 KEI Staff: Regeneron failed to disclose BARDA funding in their REGN-COV2 patent. https://www.keionline.org/34258
- **630)** 2020-10-21 Harris R: How will the limited supply of antibody drugs for COVID-19 be allocated? NPR October 21, 2020. https://www.npr.org/sections/health-shots/2020/10/21/926376342/how-will-the-limited-supply-of-antibody-drugs-for-covid-19-be-allocated

1. BARDA funds 80 percent of the R&D related to Regeneron's COVID-19 program

Regeneron has told their investors that the BARDA "is obligated to fund 80% of our costs incurred for certain research and development activities related to COVID-19 treatments." This commitment stems from the expansion of an existing contract with BARDA known as "HHSO100201700020C". ² Contract HHSO100201700020C was first established on September 29, 2017 to discover, research, develop, and manufacture antibody treatments against Ebola, Influenza, and other pathogens. ³ On January 31, 2020, BARDA and Regeneron expanded their collaboration under the HHSO100201700020C contract to include work relating to antibodies against COVID-19. ⁴

According to BARDA, the base amount awarded to Regeneron under their collaboration specifically for work related to antibodies against COVID-19 was \$82,368,277. ⁵ Since then, Regeneron has further expanded their collaboration with the U.S. government. On July 7, 2020, the Department of Defense, through an intermediary called Advanced Technology International, awarded a \$450 million contract to Regeneron, to manufacture and supply REGN-COV2. 6 The extent to which costs are shared under the \$450 million contract is unknown.

As we explain in this report, the research leading to the selection of the two antibodies that comprise the REGN-COV2 cocktail was funded with the HHSO100201700020C contract.

631) 2020-10-22 Hinton DM, FDA Chief Scientist: U.S. Food & Drug Administration Emergency Use Authorization (EUA) regarding Remdesivir. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. https://www.fda.gov/media/137564/download

Pages 1-2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury® (remdesivir) for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)³, pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. At that time, Veklury was an investigational drug and not approved for any indication.

On August 28, 2020, having concluded that revising this EUA was appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the May 1, 2020, letter in its entirety with revisions incorporated to **expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease.** In addition, the Fact Sheet for Health Care Providers was revised to provide updated clinical trial results and supporting data.⁴

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oxygenation (ECMO).", AS OF AUGUST 28, 2020, ... "expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."

On October 1, 2020, having concluded that revising this EUA was appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the August 28, 2020, letter in its entirety with revisions incorporated to the scope and conditions of authorization designating Gilead Sciences, Inc. and its authorized distributors⁵ as the responsible parties for the distribution of Velkury. On October 16, 2020, FDA reissued the October 1, 2020, letter in its entirety with revisions to clarify that an alternate care site (ACS) meeting certain criteria was considered an "inpatient hospital setting" for the purposes of the scope of the EUA, and as such, was within the terms and conditions of FDA's authorization. On October 22, 2020, FDA approved NDA 214787 for Veklury (remdesivir), which is indicated for adults and pediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Under its approval, Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the October 16, 2020, letter in its entirety with revisions to remove uses previously authorized that are now the subject of the approved NDA 214787 for Veklury, and to continue authorizing Veklury for emergency use to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

Veklury has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the data from the randomized, double-blinded, placebo controlled trial conducted by NIAID (NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), it is reasonable to believe that Veklury may be effective and the known and potential benefits of Veklury outweigh the known and potential risks of the drug for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Veklury for treatment of COVID-19, as described in the Scope of Authorization section of this reissued letter (Section II) and subject to the terms of this authorization

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¹ U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C.* § 360bbb-3. February 4, 2020.

² U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C.* § 360bbb-3, 85 FR 18250 (April 1, 2020).

³ For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

⁴ Prior to the reissuance of the EUA on August 28, 2020, and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance); (3) added hypersensitivity reaction and drug interaction information; (4) added safety information from randomized, clinical trials; (5) removed information

related to the compassionate use program; and (6) added reference to remdesivir's trade name, Veklury. ⁵ "Authorized Distributor(s)" are identified by Gilead as an entity or entities allowed to distribute authorized Veklury.

CONTRARY TO PRIOR TO AUGUST 28, 2020: "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).", AS OF AUGUST 28, 2020, ... "expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."

Page 3:

- II. Scope of Authorization I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:
 - The Veklury covered by this authorization will be used only to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg administered via intravenous (IV) infusion by a healthcare provider; and
 - The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

⁶ No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act. ⁷ Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19. ⁸ FDA's authorization includes remdesivir for injection manufactured and labeled prior to Gilead's reference to remdesivir's trade name, "Veklury", in product labeling.

ALSO, PLEASE NOTE FOOTNOTE (7) ABOVE WHICH EXPANDS THE SITES OF INFUSION FROM "ACUTE INPATIENT HOSPITAL" TO "...ARE ADMITTED OR TRANSFERRED TO AN ALTERNATE CARE SITE (ACS) THAT IS CAPABLE OF PROVIDING ACUTE CARE THAT IS COMPARABLE TO GENERAL INPATIENT HOSPITAL CARE...".

632) 2020-10-22: Farley JJ, Director, Office of Infectious Diseases, U.S. Food & Drug Administration: FDA New Drug Approval for Remdesivir NDA 214787. Letter from John Farley, MD, MPH to Ms Rhoades, Gilead Sciences, Inc. authorizing a New Drug **Authorization Approval**

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf

NDA APPROVAL 214787

Gilead Sciences, Inc. Attention: Ashley Rhoades, MBS, RAC Manager, Regulatory Affairs 333 Lakeside Drive Foster City, CA 94404

Dear Ms. Rhoades:

----- May 30, 2022 -----

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Please refer to your new drug application (NDA) dated and received August 7, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VEKLURY (remdesivir) injection, 5 mg/mL; VEKLURY (remdesivir) for injection, 100 mg/vial.

This new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

633) 2020-10-22 U.S. Food and Drug Administration: FDA News release. FDA approves first treatment for COVID-19. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

Today, the U.S. Food and Drug Administration approved the antiviral drug Veklury (remdesivir) for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Veklury is the first treatment for COVID-19 to receive FDA approval.

This approval does not include the entire population that had been authorized to use Veklury under an Emergency Use Authorization (EUA) originally issued on May 1, 2020. In order to ensure continued access to the pediatric population previously covered under the EUA, the FDA revised the EUA for Veklury to authorize the drug's use for treatment of suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. Clinical trials assessing the safety and efficacy of Veklury in this pediatric patient population are ongoing.

"The FDA is committed to expediting the development and availability of COVID-19 treatments during this unprecedented public health emergency," said FDA Commissioner Stephen M. Hahn, M.D. "Today's approval is supported by data from multiple clinical trials that the agency has rigorously assessed and represents an important scientific milestone in the COVID-19 pandemic. As part of the FDA's Coronavirus Treatment Acceleration Program, the agency will to continue to help move new medical products to patients as soon as possible, while at the same time determining whether they are effective and if their benefits outweigh their risks."

Under the Federal Food, Drug, and Cosmetic Act, approval of a new drug product requires substantial evidence of effectiveness and a demonstration of safety for the drug's intended use(s). In considering approval of a drug, the FDA conducts a benefit-risk assessment based on rigorous scientific standards to ensure that the product's benefits outweigh its risks for the intended population. This is different from the standard used in the issuance of an EUA.

The approval of Veklury was supported by the agency's <u>analysis of data</u> from three randomized, controlled clinical trials that included patients hospitalized with mild-to-severe COVID-19.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- 2020-10-22 Gilead Sciences per FDA: Highlights of prescribing information for Veklury (Remdesivir) and FULL PRESCRIBING INFORMATION. https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf
- 2020-10-22 U.S. Food and Drug Administration: Donate COVID-19 Plasma. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma
- 636) 2020-10-23 Lerner S: Trump sets up pharma billionaires for coronavirus payday. Regeneron's federally funded Covid-19 treatment, which was used to treat Donald Trump, will likely be unavailable to most patients. The Intercept. [As is stated in the yellow area below, "Regeneron...committed...to selling some of the antibodies to the government, which in turn is obligated to distribute them 'to the American people at no cost,'" according to the government's July 6 agreement, that deal applies to 'a fixed number of bulk lots." That was a year ago. On April 13, 2021, it was announced that "Roche (was) taking the lead on development of the antibody cocktail outside of the U.S."439 While REGN-COV2 is still an investigational biologic drug (monoclonal antibiotic cocktail) in the U.S. as of today, August 4, 2021, it is available to those who can obtain it in India for **59,000 Repees** (~\$800 U.S.)⁴⁷¹ | https://theintercept.com/2020/10/23/trump-covid-19pharma-regeneron-coronavirus-treatment/

Shortages Expected

Hours after the president tweeted the video, in which he said that emergency use authorization for the antibody cocktail was "all set," Regeneron applied for the fast tracking, which would make the treatment available before it has been thoroughly vetted. But the Food and Drug Administration has yet to grant the authorization.

While Regeneron initially estimated that it would have between 70,000 and 300,000 doses "as early as end of summer and completed this fall," Schleifer admitted on CBS News' "Face the Nation" that, as of October 11, it had only produced 50,000 doses, which is fewer than the number of coronavirus infections diagnosed on a single day in the U.S. last week.

And although Regeneron has committed to selling some of the antibodies to the government, which in turn is obligated to distribute them "to the American people at no cost," according to the government's July 6 agreement, that deal applies only to "a fixed number of bulk lots." After that, the pricing is up to the company — a prospect that frightens some economists.

"Executives have an interest in getting the stock price up and price gouging customers is one way they can do this," said William Lazonick, professor emeritus of economics at University of Massachusetts and co-founder of the Academic-Industry Research Network. While many drug companies argue that they use their vast profits to fund ongoing pharmaceutical innovation, Lazonick said, "we've shown that most of these companies don't do that." Instead, the soaring prices fuel soaring stock prices and executive pay, which is often based largely on that price.

The pharmaceutical industry has a long history of opposing efforts to rein in drug prices, including the "affordable pricing" clause. Regeneron was fighting that measure, which obligates

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companies that develop drugs with public money to sell them at reasonable prices, as far back as 1994.

Monoclonal antibodies are already among the most expensive pharmaceutical products available. The treatments on the market for conditions other than Covid-19 cost an average of \$96,731 per year. When used to treat cancer, the antibodies went for a median price of \$142,833, according to a 2018 study in the American Journal of Managed Care.

A Looming Nightmare

While Trump promised that the government would provide the antibody cocktail to Americans for free, drug pricing efforts say that many people probably won't have access to the treatment at all, let alone at an affordable price.

"This is a looming nightmare," said Zain Rizvi, a drug pricing expert who works at Public Citizen. "If the drug is safe and effective, the shortages will be rampant and will exacerbate the insidious inequality that's already part of our healthcare system. The privileged few may get at the head of the line and the people who need it most may not have the same opportunities."

While Rizvi said that a lack of regulation plagues the entire U.S. pharmaceutical system, he said the maker of the antibody cocktail epitomizes the administration's failure to hold companies accountable during the pandemic. "The story of Regeneron's monoclonal antibody treatment is the story of president Trump's billionaire buddy who received massive taxpayer subsidies to work on a coronavirus treatment with no strings attached," said Rizvi, who pointed out that Regeneron will be able to both set high prices for the tax-payer funded treatment and market it exclusively. "You have massive public investment, but the knowledge that comes out of it is being privatized. It doesn't benefit public health."

Already the pandemic has showcased a brutal disparity in health care. Unlike Trump, who was given two cutting-edge treatments that are inaccessible to the general public a few days after being diagnosed, patients have often had to wait for medical care when hospitals were stretched to capacity — delays that sometimes proved deadly. Although the administration has set up a fund to help cover the costs of some coronavirus treatments, many patients do not qualify. Some survivors of the disease have been hit with staggering medical bills for their treatments. And a lack of insurance is believed to have contributed to the astronomical toll of the pandemic, which has already claimed more than 223,000 lives.

For his part, Trump announced he was feeling "like perfect" after taking the Regeneron cocktail and hurried back to the White House. Once there, he helped fast-track the confirmation process of Amy Coney Barrett, his Supreme Court nominee who is widely expected to vote to strip tens of millions of Americans of their health care coverage and to outlaw the kind of research that produced the very treatment that he claims cured him.

Meanwhile, as the virus continues to surge across the country, Regeneron has said that it is continuing to produce its monoclonal antibodies and will do its best to make the treatment available to everyone.

"We are committed to ensuring that REGN-COV2 will be affordable for patients in need," Regeneron said in its emailed statement. "We know our medicines only help if people can access them, and, as such, we are working hard to develop and scale-up a completely novel treatment for COVID-19 that is accessible to the people who need it."

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For Rizvi, the reassurance rings hollow. "The corporate executives will control the price and the supply," he said. "What could go wrong?"

- 637) 2020-10-27 Regen Lab SA: Passive immune prophylaxis preventing COVID-19 with 'Acellular-Convalescent Plasma' (A-CP): a new technology introduced by Regen Lab®. https://www.prnewswire.com/in/news-releases/passive-immune-prophylaxis-preventing-covid-19-with-acellular-convalescent-plasma-a-cp-a-new-technology-introduced-by-regen-lab-r--807452422.html
- 638) 2020-10-27 Yeager A: Eli Lilly halts antibody trial in hospitalized COVID-19 patients. Recent data show that the drug bamlanivimab, also known as LY-CoV555, does not appear to help those with severe cases of COVID-19, but trials continue for milder cases. TheScientist https://www.the-scientist.com/news-opinion/eli-lilly-halts-antibody-trial-in-hospitalized-covid-19-patients-68090
- 639) 2020-10-28 Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Adams AC, Naarden J, Custer KL, Shen L, Durante M, Oakley G, Schade AE, Sabo J, Patel DR, Klekotka P, Skovronsky DM, for the BLAZER-1 Investigators. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. NEJM.org October 28, 2020; published in N Engl J Med, January 21, 2021; 384 (3): 229-237. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2029849?articleTools=true
- **640)** 2020-10-28 Regeneron: Regeneron's COVID-19 outpatient trial prospectively demonstrates that REGN-COV2 antibody cocktail significantly reduced virus levels and need for further medical attention. <a href="https://investor.regeneron.com/news-releases/news-release

REGENERON'S COVID-19 OUTPATIENT TRIAL
PROSPECTIVELY DEMONSTRATES THAT REGN-COV2
ANTIBODY COCKTAIL SIGNIFICANTLY REDUCED VIRUS
LEVELS AND NEED FOR FURTHER MEDICAL ATTENTION

TARRYTOWN, N.Y., Oct. 28, 2020 /PRNewswire/ --

Today's data, involving an additional 524 patients from the ongoing Phase 2/3 trial, provides definitive final virology results and meets the clinical endpoint of reducing medical visits

Regeneron has shared these results with the U.S. FDA, which is reviewing an Emergency Use Authorization submission for the REGN-COV2 low dose in adults with mild-to-moderate COVID-19 who are at high risk for poor outcomes

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive, prospective results from an ongoing Phase 2/3 seamless trial in the COVID-19 outpatient setting showing its investigational antibody cocktail, REGN-COV2, met the primary and key secondary endpoints. REGN-COV2 significantly reduced viral load and patient medical visits (hospitalizations, emergency room, urgent care visits and/or physician office/telemedicine visits).

"The first job of an antiviral therapeutic drug is to lower the viral load, and our initial data in 275 patients strongly suggested that the REGN-COV2 antibody cocktail could lower viral load and thereby potentially improve clinical outcomes. Today's analysis, involving more than 500 additional patients, prospectively confirms that REGN-COV2 can indeed significantly reduce viral load and further shows that these viral reductions are associated with a significant decrease in the need for further medical attention," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "We continue to see the strongest effects in patients who are most at risk for poor outcomes due to high viral load, ineffective antibody immune response at baseline, or pre-existing risk factors. Regeneron has shared these results with the U.S. Food and Drug Administration as part of its review of our Emergency Use Authorization submission, and we continue to focus on completing our ongoing trials evaluating REGN-COV2 for the treatment and prevention of COVID-19."

The randomized, double-blind trial is measuring the effect of adding REGN-COV2 to usual standard-of-care, compared to adding placebo to standard-of-care. A descriptive analysis from the first 275 patients was previously reported. Today's data, involving an additional 524 patients, show the trial met all of the first nine endpoints in the statistical hierarchy, which assessed virologic endpoints based on viral load, seronegative status and dose group, as well as the key clinical endpoint of COVID-19 related medically-attended visits, in patients who had laboratory-confirmed COVID-19 at baseline. Results showed no significant difference in virologic or clinical efficacy between the REGN-COV2 high dose (8 grams) and low dose (2.4 grams). Based on this finding, Regeneron is reviewing potential changes to dosing in the ongoing outpatient clinical trial given the current limited supply of REGN-COV2.

Virologic results (n=524, prospectively confirming previous 275-patient analysis):

641) 2020-10-28 Lilly: Lilly announces agreement with U.S. government to supply 300,000 vials of investigational neutralizing antibody bamlanivimab (LY-CoV555) in an effort to fight COVID-19. https://investor.lilly.com/node/43881/pdf

Lilly has successfully completed a Phase 1 study of bamlanivimab in hospitalized patients with COVID-19 (https://clinicaltrials.gov/ct2/show/NCT04411628). A Phase 2 study in people recently diagnosed with COVID-19 in the ambulatory setting (BLAZE-1, https://clinicaltrials.gov/ct2/show/NCT04427501) is ongoing. A Phase 3 study of bamlanivimab for the prevention of COVID-19 in residents and staff at long-term care facilities (BLAZE-2, https://clinicaltrials.gov/ct2/show/NCT04497987) is also ongoing. In addition,

https://clinicaltrials.gov/ct2/show/NC10449/98/) is also ongoing. In addition, bamlanivimab is being tested in the National Institutes of Health-led ACTIV-2 study of ambulatory COVID-19 patients.

Eli Lilly and company have twelve Clinical Trials posted as of June 1, 2021 on NIH https://clinicaltrials.gov and only one is listed as a Phase I trial (which was nominally completed

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on August 26, 2020). Therefore, as of August 26, 2020, Eli Lilly's monoclonal antibody (Ly-CoV555) bamlanivimab

https://clinicaltrials.gov/ct2/show/NCT04411628?term=eli+lilly&cond=Covid19&draw=2&rank=
4 met the criteria of the intent of PL-115-176, the Right to Try Act of 2017, which stipulates that
the only requirement that must be met so that a patient can request an Investigational Drug or
Biologic outside of a clinical trial is that a Phase I clinical trial be "completed." The nominal
completion date of NCT04411628 on NIH https://clinicaltrials.gov is August 26, 2020. While
the monoclonal antibody bamlanivimab met the criteria set forth by the FDA
https://www.fda.gov/media/72057/download and by the NIH
https://grants.nih.gov/grants/guide/notice-files/not-od-16-149.html for a completed Phase I

Clinical Trial, the FDA, the NIH, and Eli Lilly failed to notify the American public, the American
Medical profession, and the rest of the Federal Government that bamlanivimab should have been available to all Americans within 72 hours of documented contraction of COVID-19 from August
26, 2020 to the present at their request under PL-155-176, the Right to Try Law,

642) 2020-10-30 McGrail S: Eli Lilly strikes deal with Govt over COVID-19 antibody drug. HHS and DoD will purchase the first doses of the COVID-19 antibody as part of Operation Warp Speed's goals to deliver coronavirus treatments to patients by the end of 2020. PHARMANEWS INTELLIGENCE https://pharmanewsintel.com/news/eli-lilly-strikes-deal-with-govt-over-covid-19-antibody-drug

https://www.govinfo.gov/content/pkg/PLAW-115publ176/pdf/PLAW-115publ176.pdf.

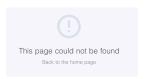
- 643) 2020-10-30 Regeneron: REGN-COV2 independent data monitoring committee recommends holding enrollment in hospitalized patients with high oxygen requirements and continuing enrollment in patients with low or no oxygen requirements.

 https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-independent-data-monitoring-committee-recommends Please note, this announcement confirms that antibody therapy should be administered early (<72 hours) in the clinical course of all individual COVID-19 positive patients.
- 644) 2020-10-30 McGrail S: Eli Lilly strikes deal with Govt over COVID-19 antibody drug. PHARMANEWS INTELLIGENCE xtelligent HEALTHCARE MEDIA. https://pharmanewsintel.com/news/eli-lilly-strikes-deal-with-govt-over-covid-19-antibody-drug
- 645) 2020-11 Simoneaux R, Shafer SL: A RAS and Bradykinin-mediated mechanism for COVID-19. ASA Monitor 2020 November; 84: 1-11. https://pubs.asahq.org/monitor/article/84/11/1/110833/A-RAS-and-Bradykinin-Mediated-Mechanism-for-COVID
- 646) 2020-11 Liu STH, Lin HM, Biane I, Wajnberg A, Gumprecht JP, Rahman F, Rodriguez D, Tandon P, Bassily-Marcus A Bander J, Sanky C, Dupper A, Zheng A, Nguyen FT, Amanat F, Stadlbauer D, Altman DR, Chen BK, Krammer F, Mendu DR, Firpo-Betancourt A, Levin MA, Bagiella E, Casadevall A, Cordon-Cardo C, Jhang JS, Arinsburg SA, Reich DL, Aberg JA, Bouvier NM: Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. Nature Medicine 2020 November; 26: 1708-1713. https://www.nature.com/articles/s41591-020-1088-9

...This retrospective, propensity score-matched case-control study assessed the effectiveness of convalescent plasma therapy in 39 patients with severe or life-threatening COVID-19 at the Mount Sinai Hospital in New York City. Oxygen requirements on day 14 after transfusion worsened in 17.9% of plasma recipients versus 28.2% of propensity score-matched controls who were hospitalized with COVID-19 (adjusted odds ratio (OR), 0.86; 95% confidence interval (CI), 0.75-0.98; chi-square test P value=0.025. Survival also improved in plasma receipients (adjusted hazard ratio (HR), 0.34; 95% CI, 0.13-0.89; chisquare test P value=0.027). Convalescent plasma is potentially effective against COVID-19, but adequately powered, randomized controlled trials are needed.

2020-11-01 Echevarria K: Remdesivir (VEKLURY) Criteria for use November 2020. U.S. Department of Veterans Affairs, Veteran Health Administration, VA Pharmacy Benefits Management Services 10P4P. https://vanf.app/CFU PDF/Remdesivir VEKLURY November2020.pdf

In my preparation of my dutiful submission in January 2022, when I attempted to access the URL above on January 5, 2022, the following came up:



When one clicks on: "Back to the home page" https://vanf.app/:

This is flagrant electronic destruction of official U.S. government documentation by a Service of an Agency of the Executive Branch of the U.S. Federal Government: VA Pharmacy Benefits Management Services 10PAP, Veterans Health Administration, U.S. Department of Veterans Affairs, which is overseen by Carolyn Clancy, M.D., M.A.C.P., VHA Deputy Under Secretary for Health (DUSH) for Discovery, Education & Affiliated Networks (DEAN). Below is the document that has been removed from the Internet that contains erroneous information in the "Inclusion Criteria."

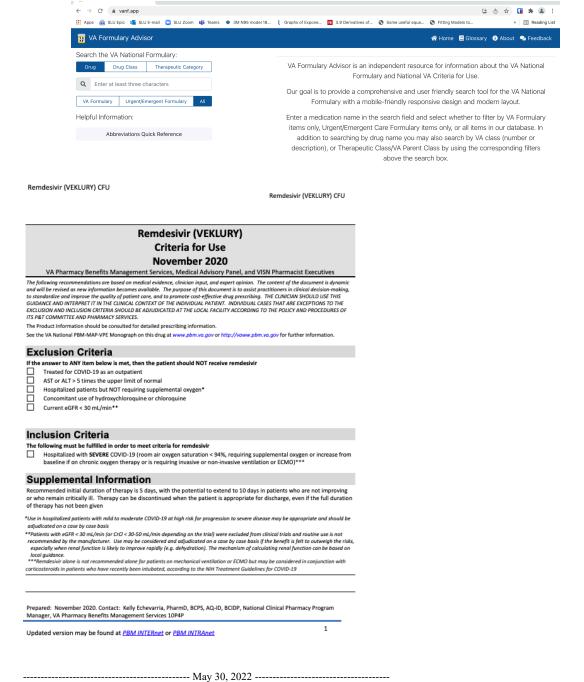
When one clicks on: "Back to the home page" https://vanf.app/:

This is flagrant electronic destruction of official U.S. government documentation by a Service of an Agency of the Executive Branch of the U.S. Federal Government: VA Pharmacy Benefits Management Services 10PAP, Veterans Health Administration, U.S. Department of Veterans Affairs, which is overseen by Carolyn Clancy, M.D., M.A.C.P., VHA Deputy Under Secretary for Health (DUSH) for Discovery, Education & Affiliated Networks (DEAN).

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Below is the document that has been removed by the VA from the Internet that contains erroneous information in the "Inclusion Criteria." THE DOCUMENT BELOW FROM THE VA Pharmacy Benefits Management Services remained under the URL above for several months! Even using the Wayback Machine, *Remdesivir (VEKLURY) Criteria for Use November 2020* cannot be found today! --Charles Andrus, M.D., F.A.C.S. 5/14/2022



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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- 648) 2020-11-03 Epstein J, Smid WM, Wendel S, Somuah D, Burnouf T: Plasma-Based COVID-19 treatments in low-and middle- income countries and the risk of transfusion-transmitted infections. Npj | Vaccines, www.nature.com/articles/s41541-020-00256-6.pdf From 1995 to 2017, Dr. Epstein was the Director, Office of Blood Research and Review, CBER, FDA. https://www.who.int/biologicals/expert committee/BIO EPSTEIN Jay 2018.pdf
- 649) 2020-11-05 Aljazeera: Regeneron hopes US will greenlight COVID-19 antibody durg soon. https://www.aljazeera.com/economy/2020/11/5/regeneron-hopes-us-will-green-light-covid-19-antibody-drug-soon

Regeron Pharmaceuticals Inc said United States health regulators were doing a careful analysis of its experimental antibody cocktail to treat COVID-19 and that it was hopeful the drug could be authorized for emergency use in the country soon. ...

...Based on clinical trials, Regeneron expects emergency use authorisation could be granted for outpatients, a group that it believes would benefit the most from the drug.

About 80,000 doses of the treatment could be ready by the end of this month, and 300,000 doses by the end of January, Regeneron said.

650) 2020-11-05 Beigel JH, Tomasek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Oh M, Ruiz-Palacios GM, Benfield T, Fatkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, and Lane HC for the ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 – Final Report. N Engl J Med 2020 Nov 5; 383 (19); 1813-1826. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764?articleTools=true

the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.) PLEASE NOTE THAT THIS STUDY WAS FUNDED "PRIMARILY" BY THE NIAID OF WHICH Dr. Fauci is the Director. FROM NOVEMBER 5, 2020, TO THE PRESENT EVERY MAN, WOMAN, AND CHILD WHO CONTRACTED COVID-19 SHOULD HAVE BEEN OFFERED REMDESIVIR AS SOON AS THEY TESTED POSITIVE.

(ABSTRACT) CONCLUSIONS Our data show that remdesivir was superior to placebo in shortening

Page 1814: ...Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase with in vitro inhibitory activity against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV),5-8 was identified early as a promising therapeutic candidate for Covid-19 because of its ability to inhibit SARS-CoV-2 in vitro.9 In addition, in nonhuman primate studies,

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remdesivir initiated 12 hours after inoculation with MERS-CoV10,11 reduced lung virus levels and lung damage.

To evaluate the clinical efficacy and safety of putative investigational therapeutic agents among hospitalized adults with laboratory-confirmed Covid-19, we designed an adaptive platform trial to rapidly conduct a series of phase 3, randomized, double-blind, placebo-controlled trials. Here, we describe the first stage of the Adaptive Covid-19 Treatment Trial (ACTT-1), in which we evaluated treatment with remdesivir as compared with placebo. The results presented here represent an update to a preliminary report after complete follow-up.

Page 1825: ...Given the preliminary results about remdesivir, the Food and Drug Administration issued an Emergency Use Authorization on May 1, 2020 (modified on August 28, 2020), to permit the use of remdesivir for treatment in adults and children hospitalized with suspected or laboratoryconfirmed Covid-19. Remdesivir has also received full or conditional approval in several other countries since that time. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients.

Page 1825: ... The trial was sponsored and primarily funded by the NIAID, National Institutes of Health (NIH), Bethesda, MD. This trial has been funded in part with federal funds from the NIAID and the National Cancer Institute, NIH, under contract HHSN261200800001E 75N910D00024, task order number 75N91019F00130/75N91020F00010, and by the Department of Defense, Defense Health Program. This trial has been supported in part by the NIAID of the NIH under award numbers UM1AI148684, UM1AI148576, UM1AI148573, UM1AI148575, UM1AI148452, UM1AI148685, UM1AI148450, and UM1AI148689. The trial has also been funded in part by the governments of Denmark, Japan, Mexico, and Singapore. The trial site in South Korea received funding from the Seoul National University Hospital. Support for the London International Coordinating Centre was also provided by the United Kingdom Medical Research Council (MRC UU 12023/23).

- 2020-11-06 Lupkin S: Federal supply deal for COVID-19 antibody treatment lacks some customary protections. NPR. https://www.npr.org/sections/healthshots/2020/11/06/931795256/federal-supply-deal-for-covid-19-antibody-treatment-lackssome-customary-protect
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- 654) 2020-11-09 Food and Drug Administration: Coronavirus (COVID-19) update: FDA authorizes monoclonal antibody for treatment of COVID-19. FDA news release, November 9, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19update-fda-authorizes-monoclonal-antibody-treatment-covid-19
- 2020-11-09 Centers for Medicare and Medicaid: Medicare monoclonal antibody COVID-19 infusion program instruction. First issued about November 12, 2020 but is not dated so this is the present version in May 2021.

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https://www.cms.gov/files/document/covid-medicare-monoclonal-antibody-infusion-program-instruction.pdf The present version gives the history of these instructions and provides for any physician to be able administer these to patients under the EUAs:

On November 9, 2020, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the investigational monoclonal antibody therapy, bamlanivimab, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients with positive COVID-19 test results who are at high risk for progressing to severe COVID-19 and/or hospitalization. Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. Review the Fact Sheet for Health Care Providers EUA of Bamlanivimabregarding the limitations of authorized use.

On November 21, 2020, the FDA issued an EUA for the investigational monoclonal antibody therapy, casirivimab and imdevimab, administered together, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients with positive COVID-19 test results who are at high risk for progressing to severe COVID-19 and/or hospitalization. As with the other monoclonal antibody infusion treatments, casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.Review the Fact Sheet for Health Care Providers EUA of Casirivimab and Imdevimab regarding the limitations of authorized use when administered together.

On February 9, 2021, the FDA issued an EUAfor the investigational monoclonal antibody therapy, bamlanivimab and etesevimab, administered together, for the treatment of mild-to-moderate COVID19 in adults and pediatric patients with positive COVID-19 test results who are at high risk for progressing to severe COVID-19 and/or hospitalization. As with the other monoclonal antibody infusion treatments, bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.Review the Fact Sheet for Health Care Providers EUA of Bamlanivimab and Etesevimab regarding the limitations of authorized use when administered together.

During the COVID-19 public health emergency (PHE), Medicare will cover and pay for these infusions (when furnished consistent with their respective EUAs) the same way it covers and pays for COVID-19 vaccines.

This would allow a broad range of providers and suppliers, including freestanding and hospital-based infusion centers, home health agencies, nursing homes, and entities with whom nursing homes contract for this, to administer these treatments in accordance with the EUA. Medicare will not pay for the COVID-19 monoclonal antibody products that providers receive for free. If providers begin to purchase COVID-19 monoclonal antibody products, Medicare anticipates setting the payment rate for the products, which will be 95% of the average wholesale price (AWP) for many health care providers, consistent with usual vaccine payment methodologies. Additionally, Medicare anticipates establishing codes and rates for the administration of the products.

In order to facilitate the efficient administration of COVID-19 vaccines to SNF residents, CMS will exercise enforcement discretion with respect to certain statutory provisions as well as any associated statutory references and implementing regulations, including as interpreted in pertinent guidance (collectively, "SNF Consolidated Billing Provisions"). Through the exercise of that discretion, CMS will allow Medicare-enrolled immunizers including, but not limited to,

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pharmacies working with the United States, as well as infusion centers, and home health agencies to bill directly and receive direct reimbursement from the Medicare program for vaccinating Medicare SNF residents.

Health care providers administering the COVID-19 monoclonal antibody infusions will follow the same enrollment process as those administering the other COVID-19 vaccines. Review provider enrollment information. https://www.cms.gov/medicare/covid-19/enrollment-administering-covid-19-vaccines

- 656) 2020-11-09 Lilly INVESTORS: Lilly's neutralizing antibody bamlanivimab (LY-CoV555) receives FDA emergency use authorization for the treatment of recently diagnosed COVID-19. https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-receives-fda
- 657) 2020-11-09 Lee SM: The FDA has authorized the COVID-19 antibody drug that Christie took—Eli Lilly's experimental coronavirus therapy, bamlanivimab, received an emergency use authorization for mild to moderate COVID-19. BuzzFeed News

 https://www.buzzfeednews.com/article/stephaniemlee/fda-coronavirus-antibody-therapy-eli-lilly
- 658) 2020-11-10 Hinton DM: Emergency Use Authorization regarding Eli Lilly's bamlanivimab. U.S. Food & drug, November 10, 2021. http://web.archive.org/web/20210123043558/https://www.fda.gov/media/143602/download
- **659)** 2020-11-10 Centers for Medicare and Medicaid: CMS takes steps to ensure medicare beneficiaries have wide access to COVID-19 antibody treatment.

 https://www.cms.gov/newsroom/press-releases/cms-takes-steps-ensure-medicare-beneficiaries-have-wide-access-covid-19-antibody-treatment This is printed *verbatim*:

Updated: November 13, 2020

The Centers for Medicare & Medicaid Services announced that starting today, Medicare beneficiaries can receive coverage of monoclonal antibodies to treat coronavirus disease 2019 (COVID-19) with no cost-sharing during the public health emergency (PHE). CMS' coverage of monoclonal antibody infusions applies to bamlanivimab, which received an emergency use authorization (EUA) from the U.S. Food and Drug Administration yesterday.

"Today, CMS is announcing a historic, first-of-its kind policy that drastically expands access to COVID-19 monoclonal antibodies to beneficiaries without cost sharing," said CMS Administrator Seema Verma. "Our timely approach means beneficiaries can receive these potentially life-saving therapies in a range of settings – such as in a doctor's office, nursing home, infusion centers, as long as safety precautions can be met. This aggressive action and innovative approach will undoubtedly save lives."

CMS anticipates that this monoclonal antibody product will initially be given to health care providers at no charge. Medicare will not pay for the monoclonal antibody products that providers

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receive for free but today's action provides for reimbursement for the infusion of the product. When health care providers begin to purchase monoclonal antibody products, Medicare anticipates setting the payment rate in the same way it set the payment rates for COVID-19 vaccines, such as based on 95% of the average wholesale price for COVID-19 vaccines in many provider settings. This means that cases that include the use of monoclonal antibody COVID-19 products will not be eligible for the enhanced payment established under the Medicare Inpatient Prospective Payment System (IPPS) in CMS-9912-IFC. CMS will issue billing and coding instructions for health care providers in the coming days.

CMS anticipates the announcement today will allow for a broad range of providers and suppliers, including freestanding and hospital-based infusion centers, home health agencies, nursing homes, and entities with whom nursing homes contract, to administer this treatment in accordance with the EUA, and bill Medicare to administer these infusions.

Under section 6008 of the Families First Coronavirus Response Act (FFCRA), state and territorial Medicaid programs may receive a temporary 6.2 percentage point increase in the Federal Medical Assistance Percentage (FMAP), through the end of the quarter in which the COVID-19 PHE ends. A condition for receipt of this enhanced federal match is that a state or territory must cover COVID-19 testing services and treatments, including vaccines and their administration, specialized equipment, and therapies for Medicaid enrollees without cost sharing. This means that this monoclonal antibody infusion is expected to be covered when furnished to Medicaid beneficiaries, in accordance with the EUA, during this period, with limited exceptions.

To view the Monoclonal Antibody COVID-19 Infusion Program Instruction, visit: https://www.cms.gov/files/document/covid-medicare-monoclonal-antibody-infusion-program-instruction.pdf

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- 662) 2020-11-11 Anwar MM, Badawi AM, Eltablawy NA: Can the coronavirus infection penetrates the brain resulting in sudden anosmia followed by severe neurological disorders? <a href="https://reader.elsevier.com/reader/sd/pii/S2405650220300691?token=2704FCAE9A6F6D340EB856A4E818BA899B840BC12513B2D39B8685B9A829472E4EB406237115DC34E3E457E8AA668EBF&originRegion=us-east-1&originCreation=20220321010145

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 https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
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 https://www.reuters.com/article/us-health-coronavirus-regeneron/regeneron-says-roche-successfully-tested-manufacture-of-covid-19-drug-used-on-trump-idUSKBN27X2T5
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 Please note that this fact sheet regarding Regeneron's monoclonal antibody cocktail exists to
 this day. The criteria for administration of casirivimab and imdevimab in the Black Box is
 stated for only in patients who have mild to moderate symptoms outside of hospital "...at
 high risk for progressing to severe COVID-19 and/or hospitalization..." This is arbitrarily
 based on a physician's ability to predict the future outcome of the individual patient
 regarding administration to or withholding from early in the disease process of the
 individual patient and has led to withholding of casirivimab and imdevimab and thus de
 facto rationing of a safe treatment that should be available to all people who become
 COVID-19 positive within 72 hours of positivity.
- 676) 2020-11-21 Regeneron: Regeneron's casirivimab and imdevimab antibody cocktail for COVID-19 is first combination therapy to receive FDA Emergency Use Authorization. https://investor.regeneron.com/news-releases/news-release-details/regenerons-regen-cov2-first-antibody-cocktail-covid-19-receive
- 677) 2020-11-23 Higgins-Dunn N: Regeneron will provide 300,000 doses of Covid treatment for U.S. by early January, CEO Schleifer says. CNBC Health and Science, published Mon, Nov 23, 2020, 10:20 AM EST, updated Mon, Nov 23, 2020, 11:14 AM EST. <a href="https://www.cnbc.com/2020/11/23/regeneron-will-provide-300000-doses-of-covid-treatment-for-us-by-early-january-ceo-schleifer-says.html#:~:text=Squawk%20Box-,Regeneron%20will%20provide%20the%20U.S.%20with%20300%2C000%20doses%20of%20its,treatment%2C%20called%20REGN%2DCOV2.

<u>Regeneron</u> will provide the U.S. with 300,000 doses of its newly authorized <u>Covid-19</u> antibody treatment by early January, the company's CEO, Dr. Leonard Schleifer, said Monday.

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The Food and Drug Administration on Saturday granted an emergency use authorization for the company's antibody treatment, called REGN-COV2. The experimental therapy was given to President Donald Trump when he contracted the coronavirus in October.

In July, the federal government, as part of the Trump administration's Operation Warp Speed, gave Regeneron \$450 million in funding to support manufacturing of the drug.

Schleifer told CNBC's "Squawk Box" on Monday that the company has 80,000 doses of its antibody treatment immediately ready for distribution. The federal government will be responsible for allocating the doses to the states "proportion to the need and amount of Covid," he said.

After January, Regeneron will have the ability to supply 100,000 doses every month, Schleifer said. The company is also conducting experiments to determine whether the dosage can be cut in half, which would eventually double the amount of available doses to 200,000 every month if proven effective, he said.

2020-11-23 Samad N, Sodunke TE, Banna HA, Sapkota A, Fatema AN, Iskandar K, Jahan D, Hardcastle TC, Nusrat T, Chowdhury TS, Haque M: Convalescent plasma therapy for management of COVID-19: Perspectives and deployment in the current global pandemic. Dovepress. https://www.dovepress.com/convalescent-plasma-therapy-formanagement-of-covid-19-perspectives-an-peer-reviewed-fulltext-article-RMHP

> Extensive review of the world literature outlining both the pros, cons, and mixed outcomes in the utilization of Convalescent Plasma.

- 679) 2020-11-24 Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vazquez C, Savoy N, Giunta, Perez LG, Sanchez M.L., Gamarnik AV, Ojeda DS, Santoro DM, Camino PJ, Antelo S, Raineo K, Vidiella GO, Miyazaki EA, Cornistein W, Trabadelo OA, Spotti M, Funtowicz G, Scordo WE, Losso MH, Ferniot I, Pardo PE, Rodriguez E, Rucci P, Pasquali J, Fuentes NA, Esperatti M, Speroni GA, Nannini EC, Matteaccio A, Michelangelo HG, Follmann D, Lane HC, Belloso W, for the PlasmAr Study Group*: A randomized trial of convalescent plasma in Covid-19 Severe Pneumonia, PlasmAR ClinicalTrials.gov number, NCT04383535. New Engl J Med, NEJM.org, DOI: 10.1056/NEJMoa2031304, November 24, 2020, 1-11. Republished by N Engl J Med, February 18, 2021; 384 (7): 619 – 629. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2031304?articleTools=true
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No differences in clinical status, outcomes

In the second <u>study</u>, a double-blind, randomized trial, a research team led by scientists with Hospital Italiano de Buenos Aires in Argentina compared the outcomes of 228 hospitalized COVID-19 patients with severe pneumonia and low oxygen levels at 12 sites who received 500 milliliters of convalescent plasma with those of 105 patients who received a placebo.

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- 689) 2020-12-09 Stolberg SG: Trump and friends got coronavirus care many others couldn't. Rudolph W. Giuliani became the latest in President Trump's inner circle to boast about the treatment he received for Covid-19, as hospitals across the country ration care. The New York Times.

https://web.archive.org/web/20201210042553/https://www.nytimes.com/2020/12/09/us/politics/trump-coronavirus-treatments.html

WASHINGTON — Ben Carson, Chris Christie and Donald J. Trump are not the sturdiest candidates to conquer the coronavirus: older, in some cases overweight, male and not particularly fit. Yet all seem to have gotten through Covid-19, and all have gotten an <u>antibody treatment</u> in such short supply that some hospitals and states are doling it out by lottery.

Now Rudolph W. Giuliani, the latest member of President Trump's inner circle to contract <u>Covid-19</u>, has acknowledged that he received at least two of the same drugs the president received. He even conceded that his "celebrity" status had given him access to care that others did not have.

"If it wasn't me, I wouldn't have been put in a hospital frankly," Mr. Giuliani, the president's personal lawyer, told WABC radio in New York. "Sometimes when you're a celebrity, they're worried if something happens to you they're going to examine it more carefully, and do everything right."

Mr. Giuliani's candid admission once again exposes that Covid-19 has become a disease of the haves and the have-nots. The treatment given to Mr. Trump's allies is raising alarms among medical ethicists as state officials and health system administrators grapple with gut-wrenching decisions about which patients get antibodies in a system that can only be described as rationing.

"We should not have Chris Christie and Ben Carson — and in the case of Carson with intervention by the president — get access," said Arthur Caplan, a medical ethicist who works with drug companies on how to ration scarce medicines, referring to the secretary of housing and urban development's admission that the president "cleared" him for the therapy. "That is not the way to secure public support for difficult rationing systems."

The treatments — a monoclonal antibody developed by Eli Lilly and a cocktail of two monoclonal antibodies developed by Regeneron — <u>won emergency use authorization</u>, or an E.U.A., from the Food and Drug Administration last month for outpatients with "mild to moderate" disease who are at high risk for progressing to severe disease or for being hospitalized.

With cases soaring, the pool of potential patients is vast.

"One of the challenges is the E.U.A. criteria really are so broad, it could be half of the people with Covid could qualify, but there is clearly not enough," said Erin Fox, the senior pharmacy director for University of Utah Health, who has helped her state draft criteria to determine who is eligible for the drugs. "Unfortunately, that leaves each hospital or each state to develop their own rationing criteria."

Even some top officials at the F.D.A. — both career employees and political appointees — have privately expressed concern in recent months that people with connections to the White House appeared to be getting access to the antibody treatments, according to three senior administration officials.

Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

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Mr. Giuliani, 76, appeared unaware of the scarcity issues, telling interviewers that politicians have taken masks and business closures too far now that Covid-19 is "a treatable disease."

In fact, the antibody treatments are so scarce that officials in Utah have developed a ranking system to determine who is most likely to benefit from the drugs, while Colorado is using a lottery system. Dr. Matthew Wynia, director of the Center of Bioethics and Humanities at the University of Colorado, said that giving the powerful access was patently unfair.

"That's one of the reasons why we decided that we would allocate this only through the state and only through this random allocation process," he said, "so that no one could get a leg up by virtue of their special connections."

And there are other complicating factors keeping many people from getting the therapies as well. The infusions must be administered in outpatient settings, but infusion centers, which also care for immune-suppressed cancer patients, are loath to treat people who have an infectious disease. And many emergency rooms are so overrun that they do not have the space.

In Utah, Dr. Fox said her hospital had shipped much of the supply of antibodies to rural hospitals, which had more room. Both she and Dr. Wynia in Colorado expressed concern that the therapies might not be distributed equitably across racial and ethnic lines, with hard-hit minority communities not getting their fair share.

The scarcity is such a problem that the National Academies of Sciences, Engineering and Medicine is holding a session next week to help medical professionals sort their way through rationing questions.

"We've been trying to get the word out so that as patients might get a positive test they could get information that they might qualify for treatment, but that only works for people with a lot of resources," Dr. Fox said.

Politicians are not the only ones with resources getting access.

In an interview on Wednesday, one prominent businessman, who spoke on condition of anonymity to avoid harming his reputation, described his aggressive efforts to track down the Regeneron treatment — including calling friends who were hospital executives and hospital donors — after he tested positive last week.

Eventually he was directed to an emergency room in his city, which was expecting him. He was given an infusion of the drug on Monday. He is feeling much better, he said.

Both Mr. Trump and Mr. Christie, a longtime friend of his and former New Jersey governor, got the antibodies before they were approved by the F.D.A. Dr. Caplan, the medical ethicist, said he had no problem with Mr. Trump, 74, getting the therapy — he is, after all, the president, "a special person unto him- or herself."

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But Mr. Christie's access appeared to be extraordinary. Mr. Christie, 58, was offered participation in a Regeneron clinical trial but turned it down, a person familiar with his treatment said, fearing he might receive a placebo. Instead, he received the Eli Lilly treatment. He is overweight and has asthma, and thus may have been a good candidate, Dr. Caplan said, though he wondered if similarly situated patients would have gotten the drug.

Dr. Carson, 69, got the Regeneron cocktail after it was approved, then took to Facebook last month to say he was "desperately ill" with the coronavirus until the president intervened.

"President Trump was following my condition and cleared me for the monoclonal antibody therapy that he had previously received, which I am convinced saved my life," he wrote, adding that "we must prioritize getting comparable treatments and care to everyone as soon as possible."

Mr. Giuliani's treatment is less clear. Calling into ABC Radio from his hospital bed on Tuesday, he said specifically that he had received two drugs — remdesivir, which has F.D.A. approval for treatment of Covid-19, and dexamethasone, a steroid.

But he also said he had received the same treatment "cocktail" as the president: "Exactly the same, his doctor sent me here; he talked me into it," Mr. Giuliani said of Mr. Trump's physician, adding, "The minute I took the cocktail yesterday, I felt 100 percent better. It works very quickly, wow."

The therapies are being allocated by the Department of Health and Human Services to states and jurisdictions based, the department's website says, on a "percentage of the country's total number of confirmed Covid-19 patients and the total number of confirmed hospitalized patients during a seven-day reporting period."

California, for example, has been allocated 17,760 doses of the Eli Lilly therapy and 5,728 doses of the Regeneron cocktail (the Eli Lilly drug is in greater supply). Maine, with many fewer people and Covid-19 cases, has been allocated 330 and 98 doses of those therapies.

Health Secretary Alex M. Azar II told reporters on Wednesday that so far, 278,000 doses of the two therapies have been allocated. There were almost that many coronavirus cases (220,225) diagnosed in the United States on Tuesday alone.

Once state and local health agencies determine which hospitals or medical facilities should get the drugs, they are shipped out by a third-party distributor. Then it is up to health care providers to figure out what to do with them. Dr. Peter L. Slavin, the president of Massachusetts General Hospital, said in an interview Tuesday that access there would be by lottery.

"The notion that we are going to be able to treat a significant percentage of the people who qualify for the drug with the drug — it's not going to happen," he said.

Noah Weiland and Katie Thomas contributed reporting.

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2020-12-20 Andrus CH: E-mail submitted to Dr. Richard Stone, M.D., Chief Medical Executive (acting Under Secretary of the Veterans Health Administration), regarding the WRONG INCLUSION CRITERIA which contradicted the FDA directive of early administration in the course of COVID-19 disease (<72 hours from diagnosis) going forward from August 28, 2020 to the present, regarding Remdesivir (an FDA -approved licensed drug: NDA# 214787). This ERRONEOUS DIRECTIVE was still published on the Internet as of October 3, 2021—not having been retracted by the Veterans Health Administration (VHA)—SHAME ON THE VHA! The URL is no longer available. https://vanf.app/CFU PDF/Remdesivir VEKLURY November2020.pdf What use to be at this U.S. Department of Veterans Affairs website is the following page that directed the administration of Remdesivir at the wrong time.

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynar and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-mak to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the	VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://voww.pbm.va.gov for further information.
Exc	lusion Criteria
	answer to ANY item below is met, then the patient should NOT receive remdesivir Treated for COVID-19 as an outpatient AST or ALT > 5 times the upper limit of normal Hospitalized patients but NOT requiring supplemental oxygen* Concomitant use of hydroxychloroquine or chloroquine Current eGFR < 30 mL/min**
Inclusion Criteria	
	Ilowing must be fulfilled in order to meet criteria for remdesivir Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
Supplemental Information	
Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration of therapy has not been given	
*Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis	
Patients with eGFR < 30 ml/min (or CrCl < 30-50 ml/min depending on the trial) were excluded from clinical trials and routine use is not recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance. *Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19	
Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P	
Updated version may be found at <u>PBM INTERnet</u> or <u>PBM INTRAnet</u> 1	

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

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IT SHOULDN'T BE THIS HARD TO SERVE YOUR COUNTRY BY DAVID SHULKIN

By Peter Nickitas, JWV National Judge Advocate

"It Shouldn't Be This Hard to Serve Your Country" describes the public service of the first Jewish-American Secretary of Veterans Affairs, Dr. David Shulkin. Shulkin served as Undersecretary of the VA from 2015 to 2017 and Secretary from 2017 to 2018. Shulkin served as the first chief medical officer of the University of Pennsylvania Health System and CEO of New York's Beth Israel Medical Center before entering public service.

This book makes outstanding reading, as Secretary Shulkin describes his encounters with entrenched officials of the Department of Veterans Affairs (VA) in his work to bring more accountability, veteran-focused care,

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

accessible service, and timely appointments. His accomplishments included updating electronic health records (EHR) systems and expanding Agent Orange treatment to Blue Water Navy veterans who served on ships off the shore of Vietnam and suffered diseases induced by the Agent Orange clouds that blew offshore. In his words, he found himself with the choice between continued neglect of veterans based on dwindling scientific evidence as veterans died, or the moral choice, and treat Blue Water Navy veterans. He took the moral choice.

He spent a great deal of energy bringing the 2014 Veteran Access, Choice, and Accountability Act up to date in 2017 and 2018, culminating in the Mission Act. At all times, he fought to ensure quality and coordinate the delegation of some care to private providers without eviscerating the core Veterans Affairs budget for VA medical center care. During his time at Secretary, he even saw patients himself at surprise appointments at VA Medical Centers.

Shulkin says his vision for the future of the VA is "a new model of governance, complete with its own board composed of health care experts, veterans, and business leaders. It should remain a government entity but with a structure that allows it to develop strategies free of political influence.... This new governance structure would mean the end of political appointees. People who serve our veterans should be chosen not on the basis of political ideology or their commitment to a particular elected individual but rather because of relevant experience, competence, and commitment to the mission."

"It Shouldn't Be This Hard to Serve Your Country" provides an example of a Jewish-American who as the founders of JWV would say, "redeems the good name of the Jew." Shulkin took the opportunity for service and made the most of it, to show that we Jewish-Americans are capable of fulfilling acts of Torah-Mitzvot and our civic obligations to our nation, our neighbors, and our fellow veterans and servicemembers, with equal fervor and merit.

Volume 74. Number 4. 2020 DECEMBER 29, 2020

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Director Wray's Statement on Violent Activity at the U.S. Capitol Building

January 7, 2021

The violence and destruction of property at the U.S. Capitol building yesterday showed a blatant and appalling disregard for our institutions of government and the orderly administration of the democratic process. As we've said consistently, we do not tolerate violent agitators and extremists who use the guise of First Amendment-protected activity to incite violence and wreak havoc. Such behavior betrays the values of our democracy. Make no mistake: With our partners, we will hold accountable those who participated in yesterday's siege of the Capitol.

Let me assure the American people the FBI has deployed our full investigative resources and is working closely with our federal, state, and local partners to aggressively pursue those involved in criminal activity during the events of January 6. Our agents and analysts have been hard at work through the night gathering evidence, sharing intelligence, and working with federal prosecutors to bring charges. Members of the public can help by providing tips, information, and videos of illegal activity at fbi.gov/USCapitol. We are determined to find those responsible and ensure justice is served.

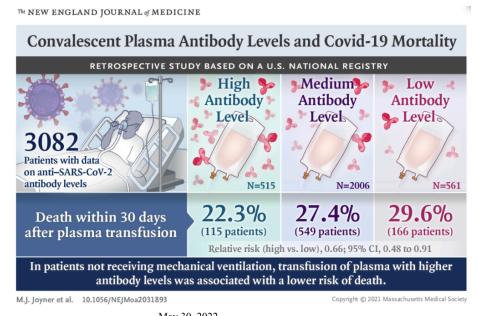
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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals Prevention: Active Immunization: Vaccines

Conclusions

Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was associated levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.

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- 717) While this URL was the posting throughout from January 15, 2021 to the present (May18, 2021) the website has changed in information. The "combatCOVID.hhs.gov" website on January 15, 2021 can be found using the Wayback Machine of the Internet Archive: http://web.archive.org/web/20210115154152/https://combatcovid.hhs.gov/i-havecovid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients . This website is explicit DHHS qualitative rationing without justification and also implicit rationing as few Americans know to access this site:

If you have COVID-19, you may be at high-risk of your symptoms getting worse. Based on your age, the length of your symptoms, and some medical conditions, you may be eligible for certain treatment or qualify for clinical studies.

WHAT IS A MONOCLONAL ANTIBODY?

Our bodies naturally make antibodies to fight infection. Monoclonal antibodies are made in a laboratory and are given to patients directly through an infusion. These treatments may help patients who are at high risk for severe illness avoid hospitalization and/or disease progression.

COVID-19 monoclonal antibody treatments are different from COVID-19 vaccines. Vaccines provide active immunity by triggering the body's natural immune response. Vaccines often require two shots and time for the body to able to develop this immune response. When you have the virus, monoclonal antibody treatments give the antibodies that the body needs to protect itself.

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AM I A CANDIDATE FOR TREATMENT?

The FDA has authorized two monoclonal antibody treatments for emergency use bamlanivimab, casirivimab and imdevimab. These treatments could help the immune system respond more effectively to the virus. Your healthcare provider can help you determine if you're a candidate for treatment.

Monoclonal antibody treatments have been authorized by the FDA for patients who have tested positive for COVID-19 in the last ten days, who are 12 years of age and older, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

This also includes people who are 65 years of age or older or who have certain chronic medical conditions.

MILESTONE

Over 600,000 monoclonal antibodies have been distributed to healthcare facilities, nationwide. DID YOU KNOW...

You're eligible to be treated with the monoclonal antibody if you are:

- 65 years of age or older
- 55 years or older with:
 - Heart disease
 - OR high blood pressure
 - OR COPD/chronic respiratory disease, including asthma.
- Any age with:
 - Obesity (a body mass index [BMI] of 35 or higher)
 - OR diabetes (Type 1 or Type 2)
 - OR chronic kidney disease
 - OR a weakened immune system
 - OR you're taking medicine that weakens your immune system

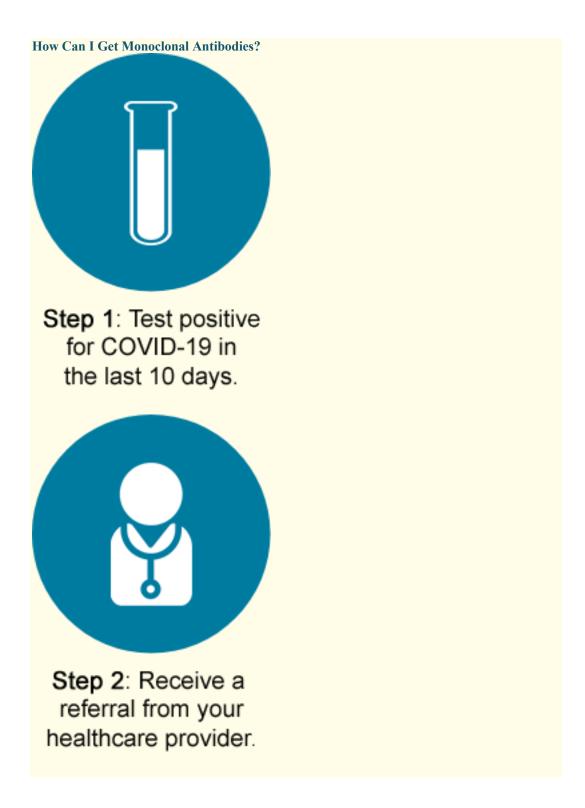
Your child is eligible to be treated with the monoclonal antibody if he or she is:

- 12 to 17 years of age and at least 40 kg (88 pounds) with:
 - Obesity (a BMI greater than or equal to 85 percent of patients of the same age and gender)
 - OR regularly uses medical technology such as a ventilator or feeding tube
 - OR have a developmental condition like cerebral palsy
 - OR sickle cell disease
 - OR congenital or acquired heart disease
 - OR asthma/chronic respiratory problems requiring daily medication for control.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals



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available infusion location.

Patients who have had symptoms for 10 days or less should be referred for treatment by their healthcare providers and directed to available infusion locations.

2021-01-15 U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. January 15, 2021.

https://web.archive.org/web/20210208223729/https://www.fda.gov/vaccines-bloodbiologics/investigational-new-drug-ind-or-device-exemption-ide-processcber/recommendations-investigational-covid-19-convalescent-plasma

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- 2021-01-19 Eban K: "A tsunami of randoms": How Trump's COVID chaos drowned the FDA in junk science. https://www.vanityfair.com/news/2021/01/how-trumps-covid-chaosdrowned-the-fda-in-junk-science
- 721) 2021-01-20 Fiore K: FDA Drowned in 'Junk Science'; sorting out COVID variants; Vax distributes chaos. MEDPAGE TODAY https://www.medpagetoday.com/publichealthpolicy/generalprofessionalissues/90789
- 2021-01-20 Perez E: Trump's acting attorney general leaves without creating controversial special counsels. CNN politics

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

https://www.cnn.com/2021/01/20/politics/justice-department-special-counsel-rosenwilkinson/index.html

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- 2021-01-21 Cohen MS: Monoclonal antibodies to disrupt progression of early Covid-19 724) infection. N Engl J Med 384;3 NEJM.org January 21, 2021. https://www.nejm.org/doi/pdf/10.1056/NEJMe2034495?articleTools=true
- 2021-01-21 Bump P: Fauci, unchained. 725) https://www.washingtonpost.com/politics/2021/01/21/fauci-unchained/
- 2021-01-21 Eli Lilly announcement to stockholders: Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. https://natap.org/2021/COVID/020321 02.htm

INDIANAPOLIS, Jan. 21, 2021 /PRNewswire/ -- Bamlanivimab (LY-CoV555) significantly reduced the risk of contracting symptomatic COVID-19 among residents and staff of long-term care facilities, Eli Lilly and Company (NYSE: LLY) announced. The Phase 3 BLAZE-2 COVID-19 prevention trial - conducted in partnership with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and the COVID-19 Prevention Network (CoVPN) - enrolled residents and staff at skilled nursing and assisted living facilities, commonly referred to as nursing homes, across the U.S. The 965 participants who tested negative for the SARS-CoV-2 virus at baseline (299 residents and 666 staff) were included in the analysis of primary and key secondary endpoints for assessing prevention, while the 132 participants (41 residents and 91 staff) who tested positive for the virus at baseline were included in exploratory analyses for assessing treatment, adding to the growing body of evidence for treatment with bamlanivimab. All participants were randomized to receive either 4,200 mg of bamlanivimab or placebo.

After all participants reached 8 weeks of follow-up, there was a significantly lower frequency of symptomatic COVID-19 (the primary endpoint) in the bamlanivimab treatment arm versus placebo (odds ratio 0.43, p=0.00021). Results for all key secondary endpoints also reached statistical significance in both the overall and resident populations.

For the pre-specified subgroup of nursing home residents, there was also a significantly lower frequency of symptomatic COVID-19 in those treated with bamlanivimab versus placebo in this important population (odds ratio 0.20; p=0.00026). These results suggest that residents randomized to bamlanivimab have up to an 80 percent lower risk of contracting COVID-19 versus residents in the same facility randomized to placebo. Results from exploratory analyses of viral load in the treatment group were consistent with previously disclosed data from BLAZE-1

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evaluating bamlanivimab as an outpatient treatment for recently diagnosed COVID-19.

Among the 299 residents in the prevention group, there were 4 deaths attributed to COVID-19 at the time of death, and all occurred in the placebo arm. There were no COVID-19 attributed deaths in the bamlanivimab arm. Among the 41 residents in the treatment group, there were 4 deaths, and all occurred in the placebo arm with none in the bamlanivimab arm. Over the entire trial, there were a total of 16 deaths reported, including deaths not related to COVID-19, and all deaths were residents (11 deaths in placebo arm and 5 in bamlanivimab arm).

"We are exceptionally pleased with these positive results, which showed bamlanivimab was able to help prevent COVID-19, substantially reducing symptomatic disease among nursing home residents, some of the most vulnerable members of our society," said Daniel Skovronsky, M.D., Ph.D., Lilly's chief scientific officer and president of Lilly Research Laboratories. "These data provide important additional clinical evidence regarding the use of bamlanivimab to fight COVID-19 and strengthen our conviction that monoclonal antibodies such as bamlanivimab can play a critical role in turning the tide of this pandemic. We're glad bamlanivimab is already available as a treatment for patients at high risk for progressing to severe COVID-19 illness or hospitalization, including those in nursing homes, and look forward to working with regulators to explore expanding the emergency use authorization to prevent the spread of COVID-19 in these facilities."

Original announcement from Lilly of January 21, 2021: https://investor.lilly.com/node/44291/pdf

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 https://investor.lilly.com/news-releases/news-release-details/new-data-show-treatment-lillys-neutralizing-antibodies
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- 737) 2021-02-01 Oxford Vaccine Group: Vaccine Knowledge Project. https://vk.ovg.ox.ac.uk/vk/covid-19-vaccines
- 738) 2021-02-01 Andrus CH:

Dear Dr. Birx:

On March 24, 2020, while there was much discussion and debate about COVID-19 convalescent plasma and the possible development of monoclonal antibodies against COVID-19, U.S. Medicine and the Government failed to explain to the American public the differences and individual utilities of *Active Immunization* (vaccines to stimulate patient antibody production) and *Passive Immunization* (provision of convalescent plasmas, convalescence sera, and immunoglobins from other species providing already formed antibodies (IgM, IgG, and IgA) against the virus in COVID-19 immunologically naïve patients immediately within 72 hours of diagnosis (testing positive).

In your interview with Margaret Brennan, you stated the following:

DR. BIRX: Well, what I do know and what was reassuring to me all along is I knew this would be studied. I knew that the emails, the reports that I wrote, the request to expand testing, the **how to improve therapeutics**,

all of that, all of that would eventually come to light. Maybe not in my lifetime.

Last summer you stated that we should collect 500,000 units of convalescent plasma to prepare for the spike in the Fall –well, we as a nation didn't do that. In fact, as you are a clinical Immunologist, you are very well aware of *Passive Immunization* in the initial early treatment (<72 hours) with the contraction of or exposure to a disease without any true alternate therapy as soon as possible (<72 hours) [e.g.: rabies, hydrops fetalis (Rhogam within 72 hours to an Rh negative mother at delivery of the prior **pregnancy**, snake bites, etc]. In fact, to withhold *Passive Immunization* (RhoGAM) from a newly delivered Rh negative mother is considered malpractice. By semantics and legal obfuscation, over the course of the last 10 months, the American public has been led down the rabbit hole by the Medical and Research community, the "Industry", and the Federal Government by not officially providing any timely-appropriate immunotherapy in the treatment of COVID-19 positivity with *Passive Immunization* until recently:

- 1. In March 2020, the FDA declared COVID-19 Convalescent Plasma *Investigational* instead of a *Biosimilar* biologic;
- 2. On March 24, 2020 the FDA outlined *Eligibility Criteria* in the late treatment of severe COVID-19 disease with COVID-19 Convalescent Plasma (at deaths door when the viremia is not the cause of death but rather the SARS pathophysiology) justifying this choice of late administration as the US did not have enough recovered convalescent patients (>14 days);
- 3. In early April 2020, the Mayo Clinic with the FDA offered COVID-19 Convalescent Plasma in the Expand Access protocol Convalescent Plasma COVID-19 (Coronavirus) Treatment (uscovidplasma.org) using the at-deathsdoor *Eligibility Criteria* ("expanded access" is really "compassionate use"—so, therefore, any resultant data cannot officially be used for completion of a Phase I Clinical Trial). Over 94,000 units of COVID-19 plasma were given AT THE THERAPEUTICALLY WRONG TIME only to severely-effected patients with the SARS pneumonitis or MSOF.
- 4. Throughout the last 11 months, the DHHS through the FDA and NIH has equated Safety Trials (Phase I trials) with Efficacy Trials (Phase II/III) so that there are no "Completed" Phase I (safety) trials with regards to COVID-19 biologics. Who should explain to the American people if the NIH plans on evading ad infinitum the "Right to Try" Law PL-115-176? Has not a bad precedent been set by not declaring a "completed" Phase I Trial with regards to COVID-19 Convalescent Plasma? Will any NIH protocol or FDA new drug/biologic Phase II/III trial and in any future research **not** be required to abide by the "Right to Try" Law, PL-115-176? In essence, the FDA and NIH are in violation, at least in violation of the intent of federal law PL-115-176 which requires a "Completed" Phase I Trial only

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for application of PL-115-176. Forcing patients to participate in Placebocontrolled Phase II/ III Trials is coercion which is prohibited by every IRB in the nation. On August 12, 2020 in the St. Louis Post-Dispatch, the following quote involving one of the FDA-Mayo Clinic's named investigators was documented:

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?"

https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/twowashington-u-doctors-lead-national-effort-to-study-new-covid-19treatment/article ccec0f56-4493-5a26-8601-45e35d364b2d.html

No IRB, worth their salt, should ever approve of such a concept of coercion in any Clinical Trial; and the FDA should not only shut down any Clinical Trial with such flagrant coercion but also censure, if not shut down, any IRB that permitted such coercion.

5. All summer, the FDA kept announcing they were close to releasing an EUA regarding COVID-19 Convalescent Plasma. President Trump went to the American Red Cross at the end of July confirming the need in his mind and that of the President's COVID-19 Taskforce for COVID-19 Convalescent Plasma. The announcement of the EUA was delayed until it would be announced on Sunday, August 23, 2020, by President Trump on the eve of the Republican National Convention. The next day, the NIH COVID-19 Guidelines Panel condemned the EUA for lacking scientific rigorous analysis (being based on Expanded Access/Compassionate Use protocol data from the FDA/Mayo clinic study). In the most-recent guidelines of the NIH COVID-19 Guideline Panel of January 14, 2021, the NIH COVID-19 Guidelines Panel is now hedging its bets by hiding under "Convalescent Plasma" Last Update October 9, 2020:

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with

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high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

(While the Mayo Clinic's Expanded Access Program (EAP) did not have an official "untreated control arm" since it was Compassionate Use only, the Mayo Clinic's EAP Safety Update in June 2020 of 20,000 patients actually included a total of 21,987 infused patients with 1,987 patients not completing the postinfusion 7-day period and 8,130 being untreated. When one back-calculates varying the possible mortality rate in this untreated group, a mortality rate of 8.7% or greater would have been statistically significant with less than a 0.05% confidence level. But, unfortunately, the Mayo Clinic's Expanded Access Program did not even qualify as a "Completed Phase I Study" by the "purism" semantics of the NIH. Dr. Birx, the FDA has final statutory say over all new drugs and biologics, **NOT** the NIH.)

- 6. The Chief Scientist of the FDA, Rear Admiral Hinton, finally removed the severity criteria by removing completely the *Eligibility Criteria* regarding Remdesivir on August 28, 2020 (the VA Central Office pharmacy formulary panel was still insisting on the severity *Eligibilty Criteria* as the only criteria for those eligible for Remdesivir in November 2020--three months after it was rescinded by Rear Admiral Hinton). Veklury (remdesivir) EUA Letter of Approval, reissued 10/22/2020 (fda.gov)
- 7. On September 2, 2020, the FDA removed completely without public awareness the severe disease *Eligibility Criteria* for COVID-19 Convalescent Plasma. Many institutions are still applying the severe disease *Eligibility Criteria* to this day-thus refusing patients COVID-19 Convalescent Plasma treatment when they first become COVID-19 positive and present to the local ER—including recently a patient with a 104 fever and uncontrollable cough that I personally know. (i.e.: The FDA's complete removal of the *Eligibility Criteria* after September 2, 2020 can be demonstrated by viewing an example of the U.S. Food & Drug Administration's website: Recommendations for Investigational COVID-19 Convalescent Plasma by comparing the most recent URL: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-ordevice-exemption-ide-process-cber/recommendations-investigational-covid-19convalescent-plasma by copying and pasting the URL into the Internet Archive (Wayback Machine) and displaying a URL before September 2, 2020 in which the severe disease *Eligibility Criteria* was outlined from April 2020 to September 2, 2020: Recommendations for Investigational COVID-19 Convalescent Plasma FDA (archive.org):

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment ProtocolExternal Link Disclaimer. These criteria include:

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation $\leq 93\%$,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio <
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.
- 8. Before the EUAs were issued by Rear Admiral Hinton regarding the Regeneron monoclonal cocktail (casirivimib and imdevimab) and Eli Lilly monoclonal antibody bamlanivimib, on October 26, 2020 Eli Lilly asked the FDA to exclude the use of their monoclonal antibody in patients with any signs of severity of associated illness parameters such as any new requirement of oxygen supplementation in any non-COPD patient or increase in amount of oxygen supplementation in COPD patients.
- 9. Rear Admiral Hinton issued EUAs for Eli Lilly's bamlanivimib (https://www.fda.gov/media/143602/download) on November 10, 2020 and for Regeneron's casirivimib and imdevimab on November 21, 2020 (https://www.fda.gov/media/143891/download). Both EUAs state the following (I will use the Regeneron's monoclonal cocktail as the example as President Trump had received this "experimental" cocktail in early October 2020 prior to the issuing of these EUAs):

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized casirivimab and imdevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply casirivimab and imdevimab to authorized distributor(s)4, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;
- The casirivimab and imdevimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
- Casirivimab and imdevimab may only be administered together;
- · Casirivimab and imdevimab is not authorized for use in the following patient populations 5:

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- Adults or pediatric patients who are hospitalized due to COVID-19, or
- Adults or pediatric patients who require oxygen therapy due to COVID19, or
- Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.
- Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
- The use of casirivimab and imdevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.
- 10. On November 24, 2020, in *NEJM* was published: Simonovich VA, *et al*: A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia (nejm.org) which is an outstanding, well-thought-out prospective trial using the discontinued/withdrawn severely-ill COVID-19 patient *Eligibility Criteria* in which all COVID-19 Convalescent Plasma was given only in patients with severe COVID-19 SARS pneumonitis. Unfortunately, the authors failed to mention in their paper's abstract conclusion that the outcome of the study was based on patients given COVID-19 Convalescent Plasma with only severe SARS pneumonitis—following the previously omitted (September 2, 2020) severe patient *Eligibility Criteria* in which *Passive Immunization* was administered at the WRONG TIME—that is at deaths-door instead of within 72-hours of COVID-19 positivity!:

CONCLUSIONS

No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. (PlasmAr ClinicalTrials.gov number, NCT04383535. opens in new tab.)

11. I wrote a Letter to the Editors of *The New England Journal of Medicine (NEJM)* regarding Simonovich VA, *et al* and included those I could access with regards to e-mails in the DHHS, the VA, and Saint Louis University SOM as I am a Professor of Surgery and the General Surgery Residency site director at the St. Louis (John Cochran) VAMC. I never got a response back from the *NEJM* but on January 6, 2021, the landmark article by Libster R, *et al*: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) demonstrated a statistically significant decrease in mortality and severity of illness in a specific age group (the elderly) when COVID-19 Convalescent Plasma was given within 72 hours (AT THE RIGHT TIME) of detection of COVID-19 positivity. As is stated in the conclusion of the abstract in this article:

CONCLUSIONS

Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Covid-19. (Funded by the Bill and Melinda Gates Foundation and the Fundación INFANT Pandemic Fund; Dirección de Sangre y Medicina Transfusional del Ministerio de Salud number, PAEPCC19, Plataforma de Registro Informatizado de Investigaciones en Salud number, 1421, and ClinicalTrials.gov number, NCT04479163.)

One of my fellow Attending Surgeons at the VA came to my office after my email cover letter to my Letter to the Editors to *NEJM* and stated that I had every right under the first Amendment to communicate whatever I wished but I was just making a fool of myself as there were much smarter people than me involved in setting standards for COVID-19 therapy. The next night, I got a call from an administrator at Saint Louis University SOM (SLUSOM) stating I was only allowed to speak about COVID-19 Convalescent Plasma with other faculty members of SLUSOM and the physicians, nurses, and other healthcare personnel at the local VA--St. Louis (John Cochran) VAMC and to STOP calling Washington DC. He then asked me unknowingly why I had included e-mails to Harvard. I responded that this e-mail was concerned my cover letter regarding my letter to the Editors of *The New England Journal of Medicine*. He responsed: Oh—speak only with those in the local VA and Saint Louis University.

[Please note I attached a slide of mortality due to COVID-19 by age range between March and November 2020. First, the mortality percentages by age range had not changed over those 9 months suggesting the USA has not diminished the death rate by any therapy employed so far in any age group over 40 years of age. Second, you will note, the mortality from 40 to 90 years increases by 0.67% per year: y = 0.0067x - 0.2647, $R^2 = 0.9676$; and, below age 40, the mortality rate increases only by 0.04% per year to maximally 0.12%/year: y=0.0004x-0.0023, R=0.7987. Once again, as the mortality rates in all range groups over the age of 40 have not changed over the last 10 months, the late administration of *Passive Immunization* to the majority of the hundred thousand patients that received COVID-19 Convalescent Plasma was given at the WRONG TIME using the now rescinded FDA patient *Eligibility Criteria*--such administration at the WRONG TIME did not make a substantial impact. What this also implies is that sending the children and young adults back to in-schoollearning will be relatively safe for the children—mortality rate 0.04% increase per year when compared with adults over age 40 years—mortality rate 0.67% per year (which is 16x higher than in children). This presents the possibility to generate a vector repository in our children who could then transmit COVID-19 to their parents, grandparents, and other adults who have a higher risk of severity of disease and death.]

12. The *NEJM* landmark article of January 6, 2021 by Libster R, *et al*: <u>Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org)</u> was overshadowed by the events that occurred later in the day in Washington

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- D.C. Ironically, on January 14, 2021, USA Today ran an article: Rodriguez A: US officials urge Americans to ask their doctors about monoclonal antibodies for COVID. But is it too little, too late? Monoclonal antibodies for COVID in full supply, but lack demand: HHS (usatoday.com). On January 17, 2021 in Infection Control Today, Kavanagh K: As Vaccine Rollout Stalls, Move Monoclonal Antibodies Into COVID Fight (infectioncontroltoday.com) using monoclonal antibodies used prophylactically to protect in exposures. **Both** monoclonal antibodies and COVID-19 Convalescent Plasma are Passive *Immunization* therapeutic agents and should therefore be administered at the same appropriate time-- <72 hours from symptomatology or COVID-19 positivity instead of only to patients at deaths-door. Over the last 10 months, the American public has been so misdirected (or lied to) by the ambiguity in the terminology and focus on vaccine production that few realize that *Passive Immunization* includes polyclonal antibodies (COVID-19 Convalescent Plasma) and monoclonal antibodies which should be given to all immediately when they become COVID-19 positive!
- 13. As is now being reported in the press, mutations of COVID-19 are developing around the World that may make the present vaccines and monoclonal antibodies ineffective.
- 14. As we go forth, the Standard-of-Care should be the following:
 - A. For those of the present 330 million Americans that are not yet infected (immunologically naïve to the disease COVID-19 negative), they should all be encouraged to receive one of the COVID-19 vaccines.
 - B. Every American who has had COVID-19 and is recovered by at least 14 days should be encouraged to donate COVID-19 Convalescent Plasma. https://www.aabb.org/for-donors-patients/give-blood
 - C. Every American who turns COVID-19 positive or becomes symptomatic (even if they have received a COVID-19 vaccine), should be afforded some form of *Passive Immunization* by the early-in-disease treatment COVID-19 Convalescent Plasma/Sera or Monoclonal Antibiodies
 - D. As the COVID-19 mutations spread and the vaccines may be less effective, every American who turns COVID-19 positive or becomes symptomatic should be afforded *Passive Immunization* of COVID-19 Convalescent Plasma/Sera matching the COVID-19 mutation. Waiting for the development of a vaccine (or monoclonal antibodies) specific for the new COVID-19 mutation and withholding mutation specific COVID-19 Convalescent Plasma would be unconceivable and tantamount to patient

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abandonment. Every time the coronavirus mutates, it will take months to develop a new vaccine or a new monoclonal antibody—yet convalescent plasma effective against every next mutation will be available 14 days after the first human recovers from each new mutation of the coronavirus through plasmapheresis donation.

E. When Kidney Transplantation was considered *Investigational* in the 1960s and 1970s and the insurance industry would not pay for Kidney Transplantation as it was "Experimental", the Congress permitted for two decades the Attending Surgeons of Washington University SOM (Drs. Newton and Anderson) and Saint Louis University SOM (Drs. Maginn, Codd, and Garvin) to perform kidney transplants on both Veterans and civilians at the John Cochran (St. Louis) VAMC. Thus, the precedent six decades ago was set to employ the largest federal hospital system (both hospitals and CBOCs) in the nation of the Veterans Health Administration (VHA) to establish infusion centers to provide *Passive Immunization* in the treatment of COVID-19 for both Veterans and civilians.

F. Thomas Jefferson's replacement of John Locke's "property" with "the pursuit of happiness" in the Declaration of Independence was no mistake. We as American physicians should be leery of any potential inherent conflict-of-interest of *Industry's* and *Medicine's* working together possibly to the detriment of our patients. De facto, Medicine, the U.S. Government, and most of the World have publicly discredited polyclonal COVID-19 Convalescent Plasma (and Sera) while elevating monoclonal antibodies as viable early treatments in COVID-19 positivity—they are both *Passive Immunization* therapies. Every time the coronavirus mutates, it will take months to develop a new vaccine or a new monoclonal antibody—yet convalescent plasma effective against every next mutation will be available 14 days after the first human recovers from each new mutation of the coronavirus through plasmapheresis donation. The present situation throughout the World today is analogous to that of the mythological Sisyphus pushing the rock up the hill only for it upon nearing the top of the hill rolling back down for eternity.

After having viewed the abridged version of your interview on January 24, 2020 (Full interview: Dr. Deborah Birx on "Face the Nation" - YouTube) with Margaret Brennan, in my eyes you have throughout your professional life been a dedicated Military and Civil Service physician for individual patients and patients in the aggregate. Both you and I are professionally of the same generation. When we graduated, you from Penn State Univ SOM in 1980 and I in 1979 from Saint Louis Univ SOM, we both swore Primum non Nocere in the care of all of our patients throughout our future lives as physicians. As I viewed the interview last Sunday, I saw a physician who loves her country and has dedicated her life as a physician to bettering all patients' lives. It is

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your duty, my duty, and all physicians' duty by our oaths of *Primum non Nocere* to advocate for not just the <u>preventative</u> measures of *Active Immunization* but also <u>all</u> potential <u>therapeutic</u> measures of *Passive Immunization*.

It would be my hope that this correspondence will be your introduction to President Biden to explain your suggestions and thoughts on our future therapy—both Active Immunization and Passive Immunization—for all Americans. As Dr. Fauci is the President's Chief Medical Advisor on the USA COVID-19 epidemic, I will forward this letter to him, the NIH, and the FDA to help facilitate your meeting with the President. My previous Letter to the Editor of The New England Journal of Medicine has not been published but was probably partially the impetus for the NEJM publishing on January 6, 2021-01-06: Libster R, et al: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) I will be sure to include the Editors of the New England Journal of Medicine in this correspondence today. Over the past year, I have submitted three items (listed below) to the U.S. Copyright Office of the Library of Congress to preserve the chronology of what has occurred for history. With any and all of my correspondence regarding our present COVID-19 epidemic, I will dutifully provide all that is asked of me by the U.S. Federal Government as it is my duty as a physician and surgeon of the Veterans Health Administration, U.S. Department of Veterans Affairs.

- 1. Andrus CH: *Time*: The Crucial Independent Variable of the COVID-19 Pandemic. U.S. Copyright Office, June 8, 2020. TXu002199029
- 2. Andrus CH: Mayo Clinic "Safety Update" should be Classified as a Completed Phase I Trial of COVID-19 Convalescent Plasma. July 22, 2020. TXu002214049
- 3. Andrus CH: 1 Dear Mr. President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. November 18, 2020. TXu002232947

On the evening of January 20, 2021, the America public was reminded of past Presidential inaugural addresses:

President Abraham Lincoln's 2nd Inaugural Address includes the lines that I, as a VA physician and surgeon, and we as Americans have promised:

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan; to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

That night, the most famous line of President Kennedy's was part of what was recited: "And so, my fellow Americas: ask not what your country can do for you—ask what you can do for you country." Dr. Birx, both you and I were in grammar school when the final lines were spoken that are most *apropos* to our present crisis and that for all time:

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My fellow citizens of the world: ask not what America will do for you, but what together we can do for the freedom of man.

Finally, whether you are citizens of America or citizens of the world, ask of us here the same high standards of strength and sacrifice which we ask of you. With a good conscience our only sure reward, with history the final judge of our deeds, let us go forth to lead the land we love, asking His blessing and His help, but knowing that here on earth God's work must truly be our own.

Dr. Birx: Godspeed.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine Chief, Unit II General Surgery (SLU GS division), St. Louis (John Cochran division) **VAMC**

Home: 314-455-9482; home e-mail: candrus600@aol.com

Beeper: 314-491-2417

My wife's, Pamela Bergkamp Andrus's, cell phone: 314-809-9634

2021-02-02 U.S. Food & Drug Administration: CLINICAL MEMORANDUM, EUA 26382, COVID-19 Convalescent Plasma (CCP). NONE OF THE VERSIONS OF THESE MEMOs are dated and thus dating was obtained from the digital captures using the Internet Archive (WayBack Machine). The URL of this Memorandaum is: https://www.fda.gov/media/141480/download

From September 1, 2020 to at least February 2, 2021 was the first iteration/rough **draft** to justify Hinton's reissuing the CCP EUA in November 2020 and then probably (the Wayback Machine has no digital captures from Feb 2 to Feb 15) the first major revision on February 4, 2021, of the CCP EUA of August 23, 2020 which was the first EUA regarding COVID-19 Convalescent Plasma issued by the FDA after the press conference announcement by President Trump of that day: Sunday, August 23, 2020—the day prior to the start of the Republican National Convention. Coincidentally, this six-month draft was the CLINICAL MEMORANDUM probably used to justify RADM Hinton's EUA of February 4, 2021 which was 48-72 hours after Dr. Andrus' Letter to Dr. Deborah Birx of February 1, 2021. As this first iteration of the MEMO regarding EUA 26382 was a draft, it lacks (1) the name of the individual who wrote it; (2) the name of the individual to whom it is written; and (3) the names of the FDA division chiefs through which the memo would pass. It does list the Sponsor, Robert Kadlec, M.D., to whom all EUAs previously have been issued regarding Remdesivir, Monoclonal Antibodies/Antibody Cocktails, and COVID-19 Convalescent Plasma (CCP).

https://web.archive.org/web/20210202143902/https://www.fda.gov/media/141480/downl

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oad The Executive Summary of the CLINICAL MEMORANDUM of September 1, 2020 through at least February 2, 2021:

EXECUTIVE SUMMARY COVID-19 Convalescent Plasma (CCP), an unapproved biological product, is proposed for use under an Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act),(21 USC 360bbb-3) as a passive immune therapy for the treatment of hospitalized patients with COVID-19, a serious or life-threatening disease. There currently is no adequate, approved, and available alternative to CCP for treating COVID-19. The sponsor has pointed to four lines of evidence to support that CCP may be effective in the treatment of hospitalized patients with COVID-19: 1) History of convalescent plasma for respiratory coronaviruses; 2) Evidence of preclinical safety and efficacy in animal models; 3) Published studies of the safety and efficacy of CCP; and 4) Data on safety and efficacy from the National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.

Considering the totality of the scientific evidence presented in the EUA, I conclude that current data for the use of CCP in adult hospitalized patients with COVID-19 supports the conclusion that CCP meets the "may be effective" criterion for issuance of an EUA from section 564(c)(2)(A) of the Act. It is reasonable to conclude that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA. Current data suggest the largest clinical benefit is associated with high-titer units of CCP administered early in the course of disease. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient populations for its use.

Recommendation: CCP meets the eligibility criteria for EUA under section 564 of the Act.

February 15, 2021 was the first digital capture of the second interation to justify the ongoing EUAs of COVID-19 Convalescent Plasma (CCP) upgrades by RADM Hinton. As this second iteration of the MEMO regarding EUA 26382 does not seem to be a draft, it contains (1) the name of the individual who wrote it; (2) the name of the individual to whom it is written; and (3) the names of the FDA divisions chiefs through which the memo would pass. It does not list the Sponsor (not yet appointed by the Biden administration and confirmed) to whom all EUAs will be issued regarding Remdesivir, Monoclonal Antibodies/Antibody Cocktails, and COVID-19 Convalescent Plasma (CCP).

http://web.archive.org/web/20210215192634/https://www.fda.gov/media/141480/downlo ad The Executive Summary of the CLINICAL MEMORANDUM from February 15, 2021 to at least April 23, 2021 (the last digital capture by the WayBack Machine) to be unchanged:

EXECUTIVE SUMMARY

COVID-19 Convalescent Plasma (CCP) was granted Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19 on August 23, 2020. At that time, the totality of the scientific evidence supported a determination that the use of CCP in hospitalized patients with COVID-19 met the "may be effective" standard for issuance of an EUA, and it was reasonable to consider that the known and potential benefits of CCP outweighed the known and potential risks for the authorized use.

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Following the EUA, emerging evidence from randomized controlled trials has continued to inform this assessment. The available evidence indicates that 1) the use of low titer CCP in hospitalized patients no longer meets the evidentiary standard of "may be effective", and 2) high titer CCP has not demonstrated benefit when administered late in the disease course in immunocompetent hospitalized patients.

Additional data from RCTs and observational studies support a determination that high titer CCP may be effective when administered early in the course of illness, particularly prior to the expected time of host antibody response. In patients with impaired humoral immunity, the potential therapeutic window may be prolonged. As RCT data continue to demonstrate that the risks of CCP do not exceed those observed with plasma transfusion in general, it is reasonable to believe that the known and potential benefits of use of high titer CCP outweigh the known and potential risks when used for the treatment of hospitalized patients with COVID-19, particularly early in the course of illness or in patients with impaired humoral immunity. Results from ongoing RCTs are expected to continue inform the optimal patient populations and product characteristics for efficacy of CCP in COVID-19.

Recommendation: The conditions of Emergency Use Authorization for CCP for the treatment of hospitalized patients with COVID-19 should be revised to exclude the use of low titer CCP. High titer CCP continues to meet criteria for Emergency Use Authorization for the treatment of hospitalized patients with COVID-19 early in the course of hospitalization. The letter of authorization and accompanying fact sheets should be revised to emphasize early administration of CCP in the absence of immunodeficiency or immunosuppression. Additional results from adequate and well-controlled trials will continue to be evaluated to further characterize the patient populations and product characteristics meeting EUA criteria.

740) 2021-02-04 Hinton DM: U.S. Food and Drug Administration Letter to Nikki Bratcher-Bowman, Acting Assistant Secretary for Preparedness and Response, EUA-update regarding COVID-19 Convalescent plasma. February 4, 2021. (Please note that the position of Assistant Secretary of Preparedness and Response changed from February 2, 2021 (48 hours previous) from Robert Kadlec, M.D. who had been appointed by President Trump to an Acting Assistant Secretary for Preparedness and Response under the Biden Administration: Nikki Bratcher-Bowman.)

https://web.archive.org/web/20210218201225/https://www.fda.gov/media/141477/download

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19 (the virus was later named SARS-CoV-2). On March 27, 2020, on the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act, subject to the terms of any authorization issued under that section.² On August 23, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with Coronavirus Disease 2019 (COVID-19), pursuant to Section 564 of the Act.³ On November 30, 2020, FDA reissued the August 23, 2020, Letter of Authorization to add a test acceptable to be used in the manufacture of COVID-19 convalescent plasma. Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2)(C) of the Act (21 U.S.C. § 360bbb-3(g)(2)(C)), FDA is again reissuing the Letter of Authorization in its entirety with revisions

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to: (1) include updates based on data from additional clinical trials; (2) clarify that the authorization is limited to use of only high titer COVID-19 convalescent plasma in hospitalized patients early in the course of disease and those hospitalized with impaired humoral immunity; (3) add the Abbott SARS-CoV-2 IgG test (ARCHITECT and Alinity i platforms), Beckman Coulter Access SARS-CoV-2 IgG test, EUROIMMUN Anti-SARS-CoV-2 ELISA (IgG) test, GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kit test, Kantaro COVID-SeroKlir test, Roche Elecsys AntiSARS-CoV-2 S test, and Siemens ADVIA Centaur SARS-CoV-2 IgG (COV2G) test as acceptable tests to be used for the purpose of qualifying high titer COVID-19 convalescent plasma in the manufacture of COVID-19 convalescent plasma; and (4) change the cutoff of the Ortho VITROS Anti-SARS-CoV-2 IgG test from S/C≥12.0 to S/C≥9.5 for qualification of COVID-19 convalescent plasma as high titer. COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. It is an investigational product and is not currently approved or licensed for any indication. The initial issuance of this EUA for COVID-19 convalescent plasma was based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the National Convalescent Plasma Expanded Access Protocol (EAP) sponsored by the Mayo Clinic. ⁵ Following the August 23, 2020 authorization, additional studies, including randomized, controlled trials, have provided data to further inform the safety and efficacy of COVID-19 convalescent plasma, and further characterize product attributes and patient populations for its use. Based on assessment of these data, potential clinical benefit of transfusion of COVID-19 convalescent plasma in hospitalized patients with COVID-19 is associated with high titer units administered early in the course of disease. ⁶ Transfusion of COVID-19 convalescent plasma in hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit. These considerations may be different in patients with suppressed or deficient humoral immunity. Therefore, this EUA is being revised to authorize only the use of high titer COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19, early in the disease course. The related fact sheets are revised accordingly. The use of low titer COVID-19 convalescent plasma is no longer authorized under this EUA.

It is reasonable to believe that the known and potential benefits of high titer COVID-19 convalescent plasma outweigh its known and potential risks for the treatment of patients hospitalized with COVID-19 early in the disease course. COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Given that the clinical evidence supporting this EUA remains limited, data from additional randomized, controlled trials are needed. Ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on the issuance of this updated EUA; providers are encouraged to enroll patients in those trials. Having concluded that the criteria for issuance of this authorization under 564(c) of the Act are met, I am authorizing the emergency use of high titer COVID-19 convalescent plasma for treatment of hospitalized patients with COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

741) 2021-02-04 U.S. Food & Drug Administration: FDA in Brief: FDA Updates Emergency Use Authorization for COVID-19 Convalescent Plasma to Reflect New Data, February 4, 2021. This is deliberate legal obfuscation on the part of the FDA by stating that it was limiting authorization—de facto, the FDA was really expanding authorization by appropriately limiting the EUA for COVID-19 Convalescent Plasma to "early in the disease course" which was contrary to FDA directives from March 24, 2020 to

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September 2, 2020 when the criteria was that CCP could *only* be given to severe patients late in the disease course. The provision of CCP late in the disease course was *de facto* perpetuated by the fact that the FDA had <u>unobtrusively removed</u> the strict severity of illness criteria late in the disease course from all FDA documentation by overwriting on September 2, 2020 and going forward on all subsequent documentation and <u>not</u> announcing it *officially* to the U.S. Medical and Research Community, probably the rest of the Federal Government, and most definitely not to the American people. The "high dose" vs "low dose" concern is a secondary issue—that was used as a distraction by the FDA--as with monoclonal antibodies/antibody cocktails, COVID-19 Convalescent Plasma and monoclonal antibodies are all *Passive Immunization* and are therapeutically identical if given *EARLY IN THE COURSE OF THE DISEASE*. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-updates-emergency-use-authorization-covid-19-convalescent-plasma-reflect-new-data

The following quote is attributed to **Peter Marks, M.D., Ph.D., Director of FDA's Center for Biologics Evaluation and Research**:

"The FDA is issuing a revision of the Emergency Use Authorization (EUA) for COVID-19 convalescent plasma as a result of our evaluation of the most recent information available. Based upon data from new clinical trials analyzed or reported since the original EUA was issued in August 2020, we have revised the EUA to limit the authorization to the use of high titer COVID-19 convalescent plasma for the treatment of hospitalized patients early in the disease course. This and other changes to the EUA represent important updates to the use of convalescent plasma for the treatment of COVID-19 patients.

"Issuance of, and updates to, EUAs are based on a thorough evaluation of currently available scientific evidence about medical products. In this case, as additional scientific evidence about COVID-19 convalescent plasma emerged, we revised the EUA to reflect the updated evidence. COVID-19 convalescent plasma used according to the revised EUA may have efficacy and its known and potential benefits outweigh its known and potential risks."

- 742) 2021-02-04. Cox D: The vaccine alternatives for people with compromised immune systems. National Geographic Science Coronavirus. February 4, 2021. https://www.nationalgeographic.com/science/article/the-vaccine-alternatives-for-people-with-compromised-immune-systems
- 743) 2021-02-04 Roxby P: Covid: 'Convalescent plasma no benefit to hospital patients.' British Broadcasting Corporation (BBC) https://www.bbc.com/news/health-55681051
- 744) 2021-02-05 REGENERON: Regeneron reports fourth quarter and full year 2020 financial and operating results. <a href="https://investor.regeneron.com/news-releases/news

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[This article is copied verbatim from the Wall Street Journal with annotations so as to translate what is meaningfully being said by those interviewed!].

The Food and Drug Administration is scaling back its authorization of the use of convalescent blood-plasma for Covid-19 patients in an effort to guide physicians who have faced a confusing thicket of data about the therapy's effectiveness.

The agency said late Thursday that the authorization, a subject of controversy since it was first issued last August, would be revised to limit the use of plasma to hospitalized patients early in the course of the disease and hospitalized patients with a medical condition that impairs their ability to make antibodies. Patients will be allowed to receive only plasma containing high concentrations of antibodies.

"The update is meant so convalescent plasma can best be used on those who will benefit," said Peter Marks, director of the FDA's Center for Biologics Evaluation and Research. "It is being used somewhat more indiscriminately." [High-titer COVID-19 Convalescent Plasma should be given to everyone becoming COVID-19 positive within <72 hours. – NOT just those hospitalized.—C. Andrus]

Dr. Claudia Cohn, chief medical officer of AABB, an organization representing the transfusion-medicine community, said the group plans to issue interim recommendations on convalescent plasma later this month. "There are so many studies coming out with different conclusions," she said. "It is not clean, it is not black and white."

Dr. Marks said the FDA reached its decision after evaluating results from several recent studies. Some showed benefits from convalescent plasma, the antibody-containing fluid derived from the blood of people who have recovered from Covid-19. Others showed no benefit.

Two clinical trials of convalescent plasma for hospitalized patients shut down last month after investigators said there appeared to be no benefit. Three trials involving hospitalized patients recently reported some benefit for the plasma, but only when given to patients soon after admission. Still another trial showed that elderly outpatients given plasma shortly after showing symptoms were less likely to develop serious disease. — [This was the January 6, 2021 publication in The New England Journal of

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Medicine which is the ONLY Prospective randomized, placebo controlled trial of CCP administration in one cohesive age group (~70 years of age). THIS IS A LANDMARK STUDY! - C. Andrus!

Arturo Casadevall, chair of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health, called the FDA decision "a step forward." He said, "Physicians in the U.S. for the first time are going to have guidance on when to use it and how to use" convalescent plasma.

Dr. Casadevall is a co-founder of the Covid-19 Convalescent Plasma Project, which helped organize a nationwide expanded-access study of convalescent plasma that began last April.

Despite the contradictory findings, convalescent plasma remains in demand—in part because there are few effective treatments for Covid-19 and many people remain unvaccinated. Since the FDA issued the emergency authorization last August, the blood industry has distributed on average about 20,600 units of convalescent plasma a week to hospitals around the country, according to the American Red Cross.

The FDA's earlier decision to authorize convalescent plasma for hospitalized Covid-19 patients was based in large part on results from an agency-sponsored expanded-access program, through which more than 72,000 patients received plasma. For a study published last month in the New England Journal of Medicine, researchers analyzed data from 3,000 of those patients and reported an apparent survival benefit among hospitalized patients not on mechanical ventilation who received plasma containing high concentrations of antibodies.

But many scientists expressed skepticism about that finding, saying expanded-access studies lack the scientific rigor of traditional trials because they have no control group to compare any apparent effect.

The FDA's Dr. Marks said the authorization of convalescent plasma "could have been handled much better. It had to do with the sense of urgency everyone is feeling. I can't blame anyone for feeling a sense of urgency." -- [As Dr. Marks is the Director of the FDA's CBER (Center for Biologics Evaluation and Research), it was his sole responsibility to have handled it better from March 2020 to the present for the biologic: COVID-19 Convalescent Plasma which is a biosimilar biologic to rabies vaccine, gamma globulin, RhoGam, hypertet, small pox convalescent plasma, IVIG, FFP, etc., etc., etc!

Dr. Marks also said the data could be confusing. Each unit of convalescent plasma is unique, reflecting the immune response of the recovered patient who donated it. It took time to figure out the best way to measure the antibodies in a unit, he added.

The U.S. isn't the only government trying to establish reliable guidelines on the use of convalescent plasma. In Argentina, a study in elderly outpatients published last month in the New England Journal of Medicine contributed to current recommendations there to treat elderly Covid-19 patients early in the course of their illness. "Plasma supplies are not endless, and invariably public health officials face difficult decisions," said study co-author Dr. Fernando Polack of

-- May 30, 2022 ----This is a COVID-19 Timeline Bibliography for Educational Purposes <u>ONLY</u> in the presentation of this information before the people of the United States of America (U.S.A.) the World and presifically the Parist of States. Fundación Infant in Buenos Aires. "In any of these decisions, guidelines based on data are necessary and are the best way for clinicians to feel comfortable when facing individual cases."

Louis M. Katz, chief medical officer of Mississippi Valley Regional Blood Center in Davenport, Iowa, which provides blood products for over 120 hospitals, said the evidence supporting the use of convalescent plasma in hospitalized patients is weak. "I think the data is there that it works early," he said. "As you move into sicker and sicker people, the evidence gets thinner and thinner."

In an editorial that accompanied the New England Journal of Medicine paper on the U.S. expanded-access study, Dr. Katz said convalescent plasma should be used only in patients early in the course of the disease. The problem with that suggestion, he later added, is the FDA emergency-use authorization still covers only hospitalized patients, who tend to show up at the hospital when they have been sick for a longer time. - [This is the problem, to become hospitalized, most patients have to be very sick and thus outside the <72 hour window! - C. Andrus, M.D.]

Treating Covid-19 patients who are just starting to show symptoms poses its own challenges. "Logistically, it is very difficult to treat patients earlier," Dr. Katz said. "It's hard to transfuse lots of plasma in outpatients." [BUT IT CAN BE DOWN IN INFUSION CENTERS or Hospital outpatient centers as is done for all infusion chemotherapies, chronic blood transfusions, etc! – C. Andrus. M.D.]

Dr. Marks said a large National Institutes of Health study is now under way to test convalescent plasma in people with Covid-19 who are sick enough to come to the emergency room but aren't admitted to the hospital, as are other randomized controlled trials of plasma in outpatients. "Until we have those data, we are going to keep the authorization to hospitalized patients," he said. "We will refine it again if appropriate. This is a scarce resource." [High-titer COVID-19] Convalescent Plasma should NOT be a scarce resource as it can be obtained twice a week from the same convalescent donor by PLASMAPHORESIS and the product from each donation will yield 2 doses (4 doses per week) and it can be stored as FFP (Fresh Frozen Plasma) for at least a year! In short, there are over 5,000 blood banks in the US so if each Blood Bank processed 20 units a day of COVID-19 Convalescent Plasma, that would be:

20 donations / day times 7 days/week times >5000 U.S. Blood Banks times 2 doses of CCP / donation = greater than 1.4 million doses per week of CCP - C. Andrus, M.D.]

> Write to Amy Dockser Marcus at amy.marcus@wsj.com Copyright ©2021 Dow Jones & Company, Inc. All Rights Reserved. 87990cbe856818d5eddac44c7b1cdeb8

Appeared in the February 6, 2021, print edition as 'FDA Limits Plasma as Treatment.'

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http://web.archive.org/web/20210416100402/https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

These is verbatim from the February 11, 2021, NIH Recommendations.

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

In the earliest stages of infection, before the host has mounted an effective immune response, anti-SARS-CoV-2 antibody-based therapies may have their greatest likelihood of having an effect. In this regard, although there are insufficient data from clinical trials to recommend either for or against the use of any specific therapy in this setting, preliminary data suggests that outpatients may benefit from receiving anti-SARS-CoV-2 monoclonal antibodies early in the course of infection. The Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for certain anti-SARS-CoV-2 monoclonal antibodies for the treatment of outpatients with mild to moderate COVID-19; please see Antibodies for more information.

Remdesivir, an antiviral agent, is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.¹⁻⁴

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest effect observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this setting.⁵⁻⁸

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

The COVID-19 Treatment Guidelines Panel (the Panel) continues to review the most recent clinical data to provide up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19. Figure 1 summarizes the Panel's recommendations for managing patients with varying severities of disease.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on **Disease Severity**

Doses and durations are listed in the footnote.

DISEASE SEVERITY PANEL'S RECOMMENDATIONS There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are Not Hospitalized, available through EUAs for outpatients who are at high risk of Mild to Moderate COVID-19 disease progression.^a The Panel recommends against the use of dexamethasone or other corticosteroids (AIII).b The Panel recommends against the use of dexamethasone (Alla) or other corticosteroids (AIII).b **Hospitalized but Does Not Require** There are insufficient data to recommend either for or against the Supplemental Oxygen routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate. Use one of the following options: **Hospitalized and Requires** Remdesivir^{c,d} (e.g., for patients who require minimal Supplemental Oxygen supplemental oxygen) (BIIa) (But Does Not Require Oxygen Delivery • Dexamethasone® plus remdesivirod (e.g., for patients who Through a High-Flow Device, require increasing amounts of supplemental oxygen) (BIII)1.9 Noninvasive Ventilation, Invasive • Dexamethasone® (e.g., when combination therapy with Mechanical Ventilation, or ECMO) remdesivir cannot be used or is not available) (BI) Hospitalized and Requires Oxygen Use one of the following options: **Delivery Through a High-Flow Device** Dexamethasone^{e,g} (Al) or Noninvasive Ventilation Dexamethasone[®] plus remdesivir^{c,d} (BIII)^{f,g} Hospitalized and Requires Invasive Dexamethasone® (AI)h Mechanical Ventilation or ECMO Rating of Recommendations: A = Strong; B = Moderate; C = Optional Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

- See the Anti-SARS-CoV-2 Monoclonal Antibodies section for more information on using bamlanivimab and casirivimab plus imdevimab in patients with
- Patients who are receiving conticosteroids for other indications should continue therapy for their underlying conditions as directed by their health care
- The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
- ⁴ For patients who are receiving rendesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, rendesivir should be continued until the treatment course is completed.
- The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
- The combination of dexamethasone and remdesivir has not been studied in clinical trials.
- In the rare circumstances where corticosteroids cannot be used, baricitinib plus remdesivir can be used (Bila). The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge
- ^h The combination of **dexamethasone** and **remdesivir** may be considered for patients who have recently been intubated (CIII). The Panel **recommends** against the use of remdesivir monotherapy in these patients.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Prevention: Active Immunization: Vaccines

mild to moderate COVID-19.

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On August 23, 2020, FDA issued an EUA for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. FDA has subsequently reissued the EUA with revisions. However, adequate and well-controlled randomized trials remain necessary for a definitive demonstration of COVID-19 convalescent plasma efficacy and to determine the optimal product attributes and appropriate patient populations for its use. Additional data will be forthcoming from other analyses and ongoing, well-controlled clinical trials. The ongoing clinical trials of investigational convalescent plasma should not be amended based on the issuance of the EUA; health care providers are encouraged to enroll patients in those trials.

. . .

III. RECOMMENDATIONS

A. Pathways for Use of Investigational Convalescent Plasma

Because convalescent plasma for the treatment of COVID-19 has not yet been approved for use by FDA, 5 it is regulated as an investigational product. As such, its administration must be under the EUA or an IND. The emergency use of COVID-19 convalescent plasma is not authorized under the EUA unless it is consistent with, and does not exceed, the terms of the Letter of Authorization, including the Scope of Authorization and Conditions of Authorization. 6 Alternatively, investigational convalescent plasma may be administered under the traditional IND regulatory pathway, a single-patient IND for emergency use, or an intermediate-size population expanded access IND (section 351(a)(3) of the PHS Act (42 U.S.C. 262(a)(3)); section 505(i) of the FD&C Act (21 U.S.C. 355(i)); 21 CFR 601.21; and 21 CFR Part 312).

FDA does not collect convalescent plasma or provide convalescent plasma. Health care providers or acute care facilities should obtain convalescent plasma from an FDAregistered or licensed blood establishment.

The following pathways are available for administering or studying the use of convalescent plasma:

1. Emergency Use Authorization

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³ Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx).

⁴ Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) (Mar. 13, 2020), available at https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-nationalemergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

⁵ Convalescent plasma is a biological product subject to the licensure requirement under section 351 of the PHS Act. 42 U.S.C. 262(a). 6 See https://www.fda.gov/media/141477/download.....

On August 23, 2020, FDA issued an EUA for COVID-19 Convalescent Plasma for the treatment of hospitalized patients with COVID-19. FDA has subsequently reissued the EUA with revisions.

Health care providers intending to administer COVID-19 convalescent plasma under the EUA are not required to report its use to FDA. Providers should refer to the Fact Sheet for Health Care Providers 7 for information on the intended use and known and potential risks and benefits of COVID-19 convalescent plasma. The Fact Sheet also provides a description of the product, information on the dosage, administration and storage of COVID-19 convalescent plasma, use in specific populations, and instructions for communicating with recipients.

As described in the Fact Sheet, health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of COVID-19 convalescent plasma, and must report fatalities to FDA as required in 21 CFR 606.170. Refer to FDA's guidance entitled "Notifying FDA of Fatalities Related to Blood Collection or Transfusion" for recommendations on reporting fatalities related to blood transfusion to FDA (Ref. 8).

2. Clinical Trials

The EUA is not intended to replace clinical trials that are critically important for the definitive demonstration of safety and efficacy of investigational convalescent plasma. Ongoing clinical trials of investigational convalescent plasma should not be amended based on the issuance of the EUA. Health care providers are encouraged to enroll patients in those trials and complete clinical trials to fully answer the questions about the effectiveness of convalescent plasma for the treatment of COVID-19.

Investigators wishing to study the use of convalescent plasma in a clinical trial should submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR Part 312). The Center for Biologics Evaluation and Research (CBER) Office of Blood Research and Review (OBRR) is committed to engaging with sponsors and reviewing such requests expeditiously. During the COVID-19 pandemic, INDs may be submitted via email to CBERDCC eMailSub@fda.hhs.gov.

Contains Nonbinding Recommendations

3. Expanded Access

An IND application for expanded access is an alternative for use of investigational convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 CFR 312.305). During the COVID-19 pandemic, INDs for expanded access, that are not single patient INDs, may be submitted via email to CBERDCC eMailSub@fda.hhs.gov.

a. Single Patient IND for Emergency Use

Given the public health emergency that the COVID-19 pandemic presents, FDA is continuing to facilitate access to investigational convalescent plasma through the process of a physician requesting a single patient IND for an individual

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⁷ See https://www.fda.gov/media/141478/download.

patient with serious or life-threatening COVID-19 under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization, if the applicable regulatory criteria are met. Note, in such cases, a licensed physician seeking to administer investigational convalescent plasma to an individual patient must request the IND (21 CFR 312.310(b)).

Note: Given that the intended use of COVID-19 convalescent plasma under the EUA is for treatment of hospitalized COVID-19 patients, FDA expects few requests for single patient INDs. FDA recommends that physicians seeking to use convalescent plasma for hospitalized COVID-19 patients should do so under the EUA and not under single patient INDs. Other options for the use of investigational convalescent plasma are listed above.

To obtain a single patient IND for emergency use, the requesting physician may contact FDA by completing Form FDA 3926 (https://www.fda.gov/media/98616/download) and submitting the form by email to CBER eIND Covid-19@FDA.HHS.gov. CBER requests that all forms be filled out electronically to facilitate rapid review. Handwritten forms are often hard to read and may delay the processing of the request. For more detailed instructions see the Form FDA 3926 Instructions (https://www.fda.gov/media/98627/download).

For requests when the provider is unable to complete and submit **Form FDA 3926** due to extenuating circumstances, or in the case of a medical emergency between the hours of 8pm and 8am Eastern Time (ET), i.e., when authorization and issuance of an IND number is needed before 8am ET the next morning, the provider should contact FDA's Office of Emergency Operations at 1-866-300-4374 to be routed to the appropriate clinical review staff for assistance with submitting the request and issuance of an IND number.

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https://physoc.onlinelibrary.wiley.com/doi/10.14814/phy2.14796

Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a world-wide pandemic with overwhelming socioeconomic impact. Since inflammation is one of the major causes of COVID-19 complications, the associated molecular mechanisms have been the focus of many studies to better understand this disease and develop improved treatments for patients contracting SARS-CoV-2. Among these, strong emphasis has been placed on pro-inflammatory cytokines, associating severity of COVID-19 with so-called "cytokine storm." More recently, peptide bradykinin, its dysregulated signaling or "bradykinin storm," has emerged as a primary mechanism to explain COVID-19-related complications. Unfortunately, this important development may not fully capture the main molecular players that underlie the disease severity. To this end, in this focused review, several lines of evidence are provided to suggest that in addition to bradykinin, two closely related vasoactive peptides, substance P and neurotensin, are also likely to drive microvascular

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permeability and inflammation, and be responsible for development of COVID-19 pathology. Furthermore, based on published experimental observations, it is postulated that in addition to ACE and neprilysin, peptidase neurolysin (Nln) is also likely to contribute to accumulation of bradykinin, substance P and neurotensin, and progression of the disease. In conclusion, it is proposed that "vasoactive peptide storm" may underlie severity of COVID-19 and that simultaneous inhibition of all three peptidergic systems could be therapeutically more advantageous rather than modulation of any single mechanism alone.

761) 2021-01-13 Fandos N: Trump acquitted of inciting insurrection, Even as bipartisan majority votes 'Guilty'. The New York Times https://www.nytimes.com/2021/02/13/us/politics/trump-impeachment.html

762) 2021-02-13 McConnell M: Mitch McConnell Speech Transcript after vote to acquit Trump in 2nd impeachment trial. Rev https://www.rev.com/blog/transcripts/mitch-mcconnell-speech-transcript-after-vote-to-acquit-trump-in-2nd-impeachment-trial

Mitch McConnell: (00:00) Mr President.

Speaker 2: (00:01) The Republican leader.

Mitch McConnell: (00:04)

January 6th was a disgrace. American citizens attacked their own government. They use terrorism to try to stop a specific piece of domestic business they did not like. Fellow Americans beat and bloodied our own police. They stormed the center floor. They tried to hunt down the Speaker of the House. They built a gallows and chatted about murdering the vice president. They did this because they'd been fed wild, falsehoods by the most powerful man on earth because he was angry. He lost an election. Former President Trump's actions preceded the riot or a disgraceful dereliction of duty. The House accused the former president of quote "Incitement". That is a specific term from the criminal law. Let me just put that aside for a moment and reiterate something I said weeks ago. There's no question, none, that President Trump is practically and morally responsible for provoking the events of the day. No question about it.

Mitch McConnell: (01:46)

The people who stormed this building believed they were acting on the wishes and instructions of their president and having that belief was a foreseeable consequence of the growing crescendo of false statements, conspiracy theories, and reckless hyperbole, which the defeated president kept shouting into the largest megaphone on planet Earth. The issue is not only the president in temperate language on January 6th. It is not just his endorsement of remarks in which an associate urged quote "Trial by combat". It was also the entire manufactured atmosphere of looming catastrophe. The increasingly wild myths about a reverse landslide election that was somehow being stolen. Some secret coup by our now president.

Mitch McConnell: (03:09)

Now I defended the president's right to bring any complaints to our legal system. The legal system spoke, the electoral college spoke. As I stood up and said, clearly at that time, the election was settled. It was over, but that just really opened a new chapter of even wilder and more unfounded claims. The leader of the free world cannot spend weeks thundering that

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shadowy forces are stealing our country and then feign surprise when people believe him and do reckless things. I sadly many politicians sometimes make overheated comments or use metaphors. We saw that. That unhinged listeners might take literally, but that was different. That's different from what we saw. This was an intensifying crescendo of conspiracy theories orchestrated by an outgoing president who seemed determined to either overturn the voter's decision or else torch our institutions on the way out. The unconscionable behavior did not end when the violence actually began.

Mitch McConnell: (04:47)

Whatever our ex president claims he thought might happen a day, whatever right reaction he's says he meant to produce by that afternoon we know he was watching the same live television as the rest of us. A mob was assaulting the Capitol in his name, these criminals who are carrying his banners, hanging his flags and screaming their loyalty to him. It was obvious that only President Trump could end this. He was the only one who could. Former aides publicly begged him to do so. Loyal allies frantically called the administration. The president did not act swiftly. He did not do his job. He didn't take steps so federal law could be faithfully executed and order restored. No, instead, according to public reports, he watched television happily as the chaos unfolded. He kept pressing his scheme to overturn the election. Now, even after it was clear to any reasonable observer that Vice President Pence was in serious danger. Even as the mob carrying Trump banners was beating cops and breaching perimeters their president sent a further tweet, attacking his own vice president.

Mitch McConnell: (07:07)

Now predictably and foreseeably under the circumstances, members of the mob seemed to interpret this as a further inspiration to lawlessness and violence not surprisingly. Later, even when the president did halfheartedly began calling for peace he didn't call right away for the riot to end. He did not tell the mob to depart until even later. And even then with police officers bleeding and broken glass covering Capitol floors, he kept repeating election laws and praising the criminals. In recent weeks, our ex-president's associates have tried to use the 74 million Americans who voted to reelect him as a kind of human shield against criticism. Using the 74 million who voted for him as kind of a human seal shield against criticism. Anyone who decries his awful behavior is accused of insulting millions of voters. That's an absurd deflection. 74 million Americans did not invade the Capitol, hundreds of rioters did. 74 million Americans did not engineer the campaign of disinformation and rage that provoked it. One person did, just one.

Mitch McConnell: (09:13)

I've made my view of this episode very plain, but our system of government gave the Senate a specific task. The Constitution gives us a particular role. This body is not invited to act as the nation's overarching moral tribunal. We're not free to work backward from whether the accused party might personally deserve some kind of punishment. Justice Joseph Story, our nations first great constitutional scholar, as he explained nearly 200 years ago, the process of impeachment and conviction is a narrow tool. A narrow tool for a narrow purpose. Story explained this limited tool exists to quote, "Secure the state against gross official misdemeanors", end quote. That is to protect the country from government officers. If President Trump were still in office, I would have carefully considered whether the House managers proved their specific charge. By the strict criminal standard the president's speech probably was not incitement.

Mitch McConnell: (10:58)

However, in the context of impeachment, the Senate might have decided this was acceptable shorthand for the reckless actions that preceded the riot. But in this case, the question is moot because former President Trump is constitutionally not eligible for conviction. Now

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this is a close question. No doubt. Donald Trump was the president when the House voted. Though, not when the House chose to deliver the paper. Brilliant scholars argue both sides of this jurisdictional question. The text is legitimately ambiguous. I respect my colleagues who've reached either conclusion. But after intense reflection, I believe the best constitutional reading shows that article two, section four, exhausts the set of persons who can legitimately be impeached, tried, or convicted. It's the president, it's the vice-president and civil officers. We have no power to convict and disqualify a former office holder who is now a private citizen.

Mitch McConnell: (12:42)

Here is article two, section four, quote, "The president, the vice-president and all civil officers of the United States shall be removed from office on impeachment for and conviction of treason, bribery, or other high crimes and misdemeanors," end quote. Now, everyone basically agrees that the second half of that sentence exhausts the legitimate grounds for conviction. The debates around the Constitution's framing make that abundantly clear. Congress cannot convict for reasons besides those. It therefore follows that the list of persons in that same sentence is also exhausted. There's no reason why one list would be exhaustive, but the other would not. Article two, section four must limit both why impeachment and conviction can occur and to whom if this revision does not limit impeachment and conviction powers then it has no limits at all. The House has sole power of impeachment and the Senate's sole power to try all impeachments, would create an unlimited circular logic empowering Congress to ban any private citizen from federal office.

Mitch McConnell: (14:25)

Now, that's an incredible claim, but it's the argument of the House managers seem to be making. One manager said the House and Senate have quote, "Absolute unqualified, jurisdictional power", end quote. Well, that was very honest because there is no limiting principle in the constitutional text that would empower the Senate to convict former officers that would not also let them convict and disqualify any private citizen, an absurd end result to which no one subscribes. Article two section four must have force. It tells us the president, the vice president, and civil officers may be impeached and convicted. Donald Trump's no longer the president. Likewise, the provision states that officers subject to impeachment and conviction shall be removed from office if convicted. Shall be removed from office, if convicted. As Justice Story explained, the Senate upon conviction is bound, in all cases, to enter a judgment of removal from office. Removal is mandatory upon conviction.

Mitch McConnell: (16:01)

Clearly he explained that mandatory sentence cannot be applied to someone who's left office. The entire process revolves around removal. If removal becomes impossible, conviction becomes insensible. In one light it certainly does seem counterintuitive that an office holder can elude Senate conviction by resignation or exploration of term, an argument we heard made by the managers. But this underscores that impeachment was never meant to be the final forum for American justice. Never meant to be the final forum for American justice. Impeachment conviction and removal are a specific intra-governmental safety valve. It is not the criminal justice system where individual accountability is the paramount goal. Indeed Justice Story specifically reminded that while former officials were not eligible for impeachment or conviction, they were, and this was extremely important, still labile to be tried and punished in the ordinary tribunals of justice. Put another way in the language of today, President Trump is still liable for everything he did while he was in office as an ordinary citizen. Unless the statute of limitations is run, still liable for everything he did while he was in office.

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Mitch McConnell: (18:04)

Didn't get away with anything, yet. Yet. We have a criminal justice system in this country. We have civil litigation and former presidents are not immune from being accountable by either one. I believe the Senate was right not to grab power the Constitution doesn't give us. And the Senate was right not to entertain some light speed sham process to try to outrun the loss of jurisdiction. It took both sides more than a week just to produce their pre-trial briefs. Speaker Pelosi's own scheduling decisions conceded what President Biden publicly confirmed, a Senate verdict before inauguration day was never possible. Now, Mr. President this has been a dispiriting time, but the Senate had done our duty. The framers' firewall helped held up again. Oh, in January the sixth, we returned to our posts and certified the election. We were uncowed. We were not intimidated. We finished the job. And since then we resisted the climber to defy our own constitutional guardrails in hot pursuit of a particular outcome.

Mitch McConnell: (19:48)

We refused to continue a cycle of recklessness by straining our own constitutional boundaries in response. The Senate's decision today does not condone anything that happened on or before that terrible day. It simply shows that senators did what the former president failed to do. We put our constitutional duty first.

763) 2021-02-16 Wosinska M, Zavodszky A, Romine M, McClellan M: Promising practices for promoting utilization of COVID-19 monoclonal antibody treatments. Duke Margolis Center for Health Policy, February 16, 2021.

https://healthpolicy.duke.edu/sites/default/files/2021-02/Promising%20Practices%20for%20Promoting%20Utilization%20of%20COVID-19%20Monoclonal%20Antibody%20Treatmentsv4.pdf

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- 2021-02-16 Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, Huhn G, Cardona J, Mocheria B, Stosor V, Shawa I, Kumar P, Adams AC, van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM: Effect of Bamlanivimab as monotherapy or in combination with Estevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. JAMA 2021 Feb 16; 325 (7): 632-644. file:///Users/andrusmd/Downloads/jama gottlieb 2021 oi 210002 1613412631.85755%20(2).pdf

MAIN OUTCOMES AND MEASURES The primary end point was change in SARS-CoV-2 log viral load at day 11 (±4 days). Nine prespecified secondary outcome measures were evaluated with comparisons between each treatment group and placebo, and included 3 other measures of viral load, 5 on symptoms, and 1 measure of clinical outcome (the proportion of patients with a COVID-19-related hospitalization, an emergency department [ED] visit, or death at day 29).

RESULTS Among the 577 patients who were randomized and received an infusion (mean age, 44.7 [SD, 15.7] years; 315 [54.6%] women), 533 (92.4%) completed the efficacy evaluation period (day 29). The change in log viral load from baseline at day 11 was -3.72 for 700 mg, -4.08

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for 2800 mg, -3.49 for 7000mg, -4.37 for combination treatment, and -3.80 for placebo. Compared with placebo, the differences in the change in log viral load at day 11were 0.09 (95% CI, -0.35) to 0.52; P = .69) for 700 mg, -0.27 (95% CI, -0.71 to 0.16; P = .21) for 2800 mg, 0.31 (95% CI, -0.13 to 0.76; P = .16) for 7000 mg, and -0.57 (95% CI, -1.00 to -0.14; P = .01) for combination treatment. Among the secondary outcome measures, differences between each treatment group vs the placebo group were statistically significant for 10of84endpoints. The proportion of patients with COVID-19-related hospitalizationsorEDvisitswas5.8% (9events) for placebo, 1.0% (1event) for 700mg, 1.9% (2events) for 2800 mg, 2.0% (2 events) for 7000 mg, and 0.9% (1 event) for combination treatment. Immediate hypersensitivity reactions were reported in 9 patients (6 bamlanivimab, 2 combination treatment, and 1 placebo). No deaths occurred during the study treatment.

CONCLUSIONS AND RELEVANCE Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for bamlanivimab monotherapy. Further ongoing clinical trials will focus on assessing the clinical benefit of antispike neutralizing antibodies in patients with COVID-19 as a primary end point.

TRIAL REGISTRATION Clinical Trials.gov Identifier: NCT04427501

2021-02-16 U.S. Food & Drug Administration: Clinical Memorandum. COVID-19 Convalescent Plasma EUA Decision Memo. https://www.fda.gov/media/141480/download is the baseline URL which when placed in the Wayback Machine, 8-23-2020 to 2-2021 is the renewed new memo on CCP EUA issued 2-2021 to the present: https://web.archive.org/web/20210330024720/https://www.fda.gov/media/141480/download

EXECUTIVE SUMMARY

COVID-19 Convalescent Plasma (CCP) was granted Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19 on August 23, 2020. At that time, the totality of the scientific evidence supported a determination that the use of CCP in hospitalized patients with COVID-19 met the "may be effective" standard for issuance of an EUA, and it was reasonable to consider that the known and potential benefits of CCP outweighed the known and potential risks for the authorized use.

Following the EUA, emerging evidence from randomized controlled trials has continued to inform this assessment. The available evidence indicates that 1) the use of low titer CCP in hospitalized patients no longer meets the evidentiary standard of "may be effective", and 2) high titer CCP has not demonstrated benefit when administered late in the disease course in immunocompetent hospitalized patients.

Additional data from RCTs and observational studies support a determination that high titer CCP may be effective when administered early in the course of illness, particularly prior to the expected time of host antibody response. In patients with impaired humoral immunity, the potential therapeutic window may be prolonged. As RCT data continue to demonstrate that the risks of CCP do not exceed those observed with plasma transfusion in general, it is reasonable to believe that the known and potential benefits of use of high titer CCP outweigh the known and potential risks when used for the treatment of hospitalized patients with COVID-19, particularly early in the course of illness or in patients with impaired humoral immunity. Results from ongoing RCTs are expected to continue inform the optimal patient populations and product

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characteristics for efficacy of CCP in COVID-19.

Recommendation: The conditions of Emergency Use Authorization for CCP for the treatment of hospitalized patients with COVID-19 should be revised to exclude the use of low titer CCP. High titer CCP continues to meet criteria for Emergency Use Authorization for the treatment of hospitalized patients with COVID-19 early in the course of hospitalization. The letter of authorization and accompanying fact sheets should be revised to emphasize early administration of CCP in the absence of immunodeficiency or immunosuppression. Additional results from adequate and well-controlled trials will continue to be evaluated to further characterize the patient populations and product characteristics meeting EUA criteria

Antibody responses in COVID-19 and timing of CCP transfusion

The relative roles of humoral and cellular immunity in SARS-CoV-2 infection continue to be unraveled, and it appears likely that CD4+ T cells, CD8+ T cells, and neutralizing antibody responses all contribute to control of SARS-CoV-2 infection in both non-hospitalized and hospitalized cases of COVID-19[23]. The large majority of patients with SARS-CoV-2 infection will seroconvert within 5-15 days post-symptom onset, with 90% seroconverting by day 10[23-25]. IgM and IgG antibodies are frequently detected concurrently[26], and peak anti-spike or anti-RBD IgG levels are reached by approximately 15 days post symptom onset[27]. Antibody responses and memory B cells appear to persist for at least 5 months and antibodies may be a correlate of immune protection[28-31]. Delayed antibody response kinetics also appear to be associated with more severe disease[27, 32]. At the same time, studies have generally shown higher titers in patients following recovery from severe disease compared to mild or asymptomatic illness[25, 33].

The observation that high titer CCP was beneficial when administered within 72 hours of symptom onset in high risk subjects, but failed to demonstrate benefit in trials where the median duration of symptoms was 8 days or longer, indicates benefit with CCP transfusion is more likely in patients early in the humoral immune response when host antibody titers remain undetectable or low (i.e., likely within the first week following symptom onset) This is consistent with longstanding historical precedent in passive immune therapies for viral infections, where prophylactic or early use has generally been more effective than in established infections[34].

These trends are also consistent with clinical evidence for administration of anti-SARS-CoV-2 monoclonal antibodies, where benefit has been demonstrated with early outpatient use, but not in hospitalized patients within 12 days of symptom onset[35-37] as described in the following two studies:

In outpatient studies of bamlanivimab in recently diagnosed patients with mild to moderate disease (BLAZE-1)[36], subjects were excluded if they were previously known to be seropositive. Subjects had a median of 4 days of symptoms at the time of infusion, and the study found one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time. While reduction in viral load was the primary endpoint in this phase 2 trial, subjects treated with bamlanivimab also showed a nominally statistically significant reduction in COVID-19 related hospitalizations or ED visits within 28 days in the pooled dose-level data.

In outpatient studies of casirivimab/imdevimab in symptomatic patients with mild to moderate COVID-19 (R10933-10987-COV-2067), subjects who were no more than 7 days from symptom enrollment were included regardless of serostatus[35]. Casirivimab/imdevimab treatment

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reduced viral load, and patients who were seronegative at baseline showed larger reductions in viral load and a larger reduction in the proportion of subjects with at least one medically attended visit compared to the overall population. Based on these studies, both therapies were granted EUA for use in high risk outpatients with mild to moderate COVID-19 (https://www.fda.gov/media/143892/download, https://www.fda.gov/media/143603/download).

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In early studies of the COVID-19 pandemic, the median time from symptom onset to the development of dyspnea was approximately 5-8 days[38, 39], and patients who develop critical illness typically do so shortly thereafter (days 8-10)[40]. While the study by Libster et al[10] demonstrated a reduction in progression to severe disease in high risk outpatients within 72 hours of the onset of symptoms, one factor complicating very early use of CCP in the outpatient population is the evidence that a large proportion of these patients will have a self-limited illness and will not go on to severe or critical illness even without targeted intervention[41]. Therefore, in the early-disease outpatient population, it is important to have a full understanding of the relative benefit and identify high-risk populations so that the known and potential risks of transfusion are outweighed by the known and potential benefits of CCP. Ongoing randomized controlled trials will be critical to determine the clinical and laboratory parameters that can identify where the potential benefit of CCP outweighs the potential risk in outpatients.

Based on the study by Libster et al[10] the therapeutic window appears to be at least within 72 hours of symptom onset, while additional negative RCTs with a median duration of symptoms prior to transfusion of 8 days indicating that 8 days after symptom onset may be too late for efficacy of CCP in immunocompetent hospitalized COVID-19 patients. These timepoints appear to correlate with the timing of the patients' own antibody responses to infection, such that by the time a patient is forming their own antibodies, benefit from CCP appears unlikely. The time period between 3 and 7 days remains to be studied rigorously in randomized trials of CCP, but observational studies, preclinical studies, studies of related therapies, and what is known about the timing of the adaptive immune response in SARS-CoV-2 infection suggest that high titer CCP may be effective in this window period. As noted above, this window appears to be longer in the setting of impaired or deficient humoral immunity. Nonetheless, adequate and well controlled trials in this time period remain necessary for a conclusive demonstration of efficacy.

- 767) 2021-02-16 Centers for Disease Control and Prevention: Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Most recent update.
 - http://web.archive.org/web/20210408021730/https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
- 768) 2021-02-17 Wilt TJ, Kaka AS, MacDonald R, Linskens E, Obley A, Vela K, Duan-Porter W: COVID-19: Remdesivir for Adults A Living Review. Updated February 2021, Health Services Research & Development Service, U.S. Department of Veterans Affairs. https://web.archive.org/web/20210319093451/https://www.hsrd.research.va.gov/publications/esp/covid-19-remdesivir.cfm
- **769)** 2021-02-17 Sauber R: Letter to Michael R. Hogan, Designated Agency Ethics Official...In a letter of February 17, 2021.

https://extapps2.oge.gov/201/Presiden.nsf/PAS+Index/249BEDEAC38845E48525868D0032DC51/\$FILE/Sauber,%20Richard%20%20finalEA.pdf

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770) 2021-02-18 Katz LM: (A Little) Clarity on convalescent plasma for Covid-19. Initially published on January 13, 2021) This editorial was republished in the N Engl J Med, 2021 Feb 18; 384 (7): 666 – 668. https://www.nejm.org/doi/full/10.1056/NEJMe2035678 In the article, it was not disclosed that Dr. Katz is the Chief Medical Director, ImpactLife: https://www.bloodcenter.org/about/news/authors/dr-louis-katz-a4/

[Please note that Dr. Katz was not fully identified by this paper. Dr. Katz is "...the former Chief Medical Officer at America's Blood Centers in Washington, DC, an ABC past president, former board member and a past chair of its Scientific, Medical and Technical Committee. His transfusion medicine career has been dominated by attention to transfusion transmitted infections. He has served multiple terms as the chair of the AABB Transfusion Transmitted Diseases committee and served on many AABB committee and working groups. Dr. Katz is on the Editorial Board of the journal Transfusion, has served on the FDA Blood Products Advisory Committee as a member, industry representative and chair, and is a current member of the HHS Advisory Committee on Blood and Tissue Safety and Availability." – Winn KI, Katz L, Goel R: Dr. Louis Katz, Acting Chief Medical Director. ImpactLife (formerly Mississippi Valley Regional Blood Center). https://www.bloodcenter.org/about/news/authors/dr-louis-katz-a4/]

The text of this article that follows is verbatim because it explains the mindset of those involved in the FDA's, NIH's, and The White House's convoluted obfuscation in the lack of treatment during the viremic phase of those infected with COVID-19 with passive immunization (Covid-19 Convalescent Plasma [CCP]) AND THE COVER-UP by US Medicine and the US Government THAT HAS BEEN PERVASIVE OVER THE LAST 15 months. While advocating for the appropriate administration early in the viremic phase of Covid-19 (<72 hours from symptoms/diagnosis) in the outpatient setting and NOT IN THE HOSPITAL SETTING, this New England Journal of Medicine editorial fails strongly to emphasis the definitive utility of PASSIVE IMMUNIZATION and thus has been ignored by the medical community, the US federal government, and the US public-at-large. Even after the FDA quietly removed from all its official documentation on 9/2/2020 mandating the strict erroneous CCP administration critera initiated by the FDA / vis-à-vis The White House on March 24, 2020 for use only in severely affected patients--late in the disease--administration of CCP (during the cytokine cascade and bradykinin phase which both are dominant in severely hospitalized patients and then only somewhat effective treatment is supportive) continued. The wrong-time administration of CCP became the de facto standard-of-care. The majority of 722,000 doses of CCP given over the last 15 months to individuals late in their disease course throughout the U.S.A. (and much of the World) was given at the WRONG TIME. -

And the FDA, the NIH, the VA, *The White House*, the *New England Journal of Medicine*, etc. <u>knew it!</u>

PASSIVE IMMUNOTHERAPY has been used since the late 19th century, and in 1901, the first Nobel Prize in Physiology or Medicine was awarded for serum therapy for patients with diphtheria. During the 1918 pandemic, serum from convalescent patients was used to treat influenza, with some apparent success. I Today, the use of immunoglobulins has been established for the prophylaxis and treatment of a variety of infections, including those with respiratory syncytial virus, cytomegalovirus, and hepatitis B or hepatitis A virus. More recently, passive immunotherapy has been evaluated for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and Ebola virus disease. Intravenous human immunoglobulin has revolutionized the management of immunoglobulin deficiency states.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

The use of convalescent plasma against SARS coronavirus 2 (SARS-CoV-2) is advocated for the treatment of patients with coronavirus disease 2019 (Covid-19). The experience with influenza A is relevant, and a meta-analysis suggested that early treatment, before critical illness develops, may be an important predictor of the efficacy of passive immunotherapy for that pathogen. 1 The authors of that meta-analysis acknowledged the low quality of the available evidence regarding early treatment. Another meta-analysis of studies of convalescent plasma and hyperimmune immunoglobulin in patients with influenza A and SARS suggested a mortality benefit "when convalescent plasma is administered early after symptom onset." 2 However, in a randomized, controlled trial, high-titer convalescent plasma from patients who had recovered from H1N1 influenza was ineffective against severe influenza A infection in hospitalized children and adults.3

Initial randomized trials of convalescent plasma in patients with Covid-19 focused on hospitalized patients who were already moderately to severely ill, and these trials provided weak evidence of clinical efficacy. 46 Some were underpowered when nonpharmaceutical interventions such as masking and social and physical distancing reduced the incidence of Covid-19 and enrollment was limited. Also, these trials were heterogeneous with respect to the characteristics of the convalescent plasma used (e.g., its antibody content and the stratification of the recipients according to their serologic status). No unexpected safety signals beyond the recognized risks of plasma transfusion (i.e., fluid overload, transfusion-associated acute lung injury, and allergy) have emerged, nor has there been evidence of antibody-dependent enhancement of Covid-19 severity. Accordingly, it is difficult to make actionable conclusions about the clinical value of convalescent plasma.

Observational studies have been more positive than randomized trials; some, but not all, of these studies have suggested modest clinical effects and measurable surrogate virologic outcomes. 7.8 They have confirmed the safety profile of plasma transfusions but have some of the same issues as randomized trials, in addition to the potential biases and shortcomings inherent in observational studies.

The Food and Drug Administration (FDA) argued that a "totality of the evidence" suggested that the benefits of convalescent plasma would outweigh its risks, and given the lack of effective treatments, the FDA granted an Emergency Use Authorization (EUA) and provided guidance on the manufacture and use of convalescent plasma in hospitalized patients with signs of **progressive infection.** By contrast, a National Institutes of Health guidelines panel stated that "the data are insufficient to recommend for or against" the use of convalescent plasma. The Infectious Diseases Society of America and the AABB (formerly known as the American Association of Blood Banks) recommend that the use of convalescent plasma be limited to clinical trials, that critically ill patients and those in the intensive care unit (ICU) are unlikely to benefit from transfusions of convalescent plasma, and that convalescent plasma should be used as early as possible in the course of infection (preferably within 3 days after diagnosis) in order to achieve the best outcomes.9

Considering the number of SARS-CoV-2 infections, the paucity of treatment options, and the enthusiasm for and controversy about convalescent plasma, a high-quality, multicenter, randomized, controlled trial is most welcome. Libster and colleagues now report in the Journal¹⁰ the results of a well-executed trial of early convalescent plasma in older adult patients in whom symptomatic SARS-CoV-2 infection was diagnosed with the use of a polymerase-chain-reaction assay. In this double-blind trial, 250 ml of convalescent plasma with an IgG titer greater than 1:1000 against SARS-CoV-2 spike (S) protein was compared with saline placebo in patients who were 65 to 74 years of age and had prespecified

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coexisting conditions and in patients who were 75 years of age or older with or without coexisting conditions.

The patients received convalescent plasma or placebo less than 72 hours after symptom onset. In the intention-to-treat population, a primary end-point event (progression to predefined severe disease during follow-up) occurred in 16% (13 of 80 patients) and 31% (25 of 80 patients) of the well-matched convalescent plasma and placebo groups, respectively. A dose-dependent effect relative to the antibody titers after infusion was observed, and this effect was larger after the exclusion of 6 patients who had a primary end-point event before infusion. The benefits of convalescent plasma with respect to the secondary end points were consistent with those associated with the primary end point. No serious adverse events were observed. The authors conclude that "early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19." Even before the current trial, the EUA emphasized the potential advantages of early therapy with high-titer convalescent plasma. Unfortunately, a direct comparison of antibody levels in the current trial with assays specified in the FDA EUA is not available. Antibody titers in the recipients at enrollment were not provided, so no comment can be made about the usefulness of seroreactivity in patients as a criterion for convalescent plasma use.

At this time, convalescent plasma should be reserved for patients in whom the duration, severity, and risk of progression of illness are similar to those in the patients in this trial. Younger high-risk patients (and certain immunodeficient patients) with these disease characteristics should be considered as well.

The supply of convalescent plasma has been tenuous during the marked increase in Covid-19 cases during the fall in the United States, although recent collections have improved. From September 28 through December 27, 2020, distributions of new and stockpiled units of convalescent plasma to hospitals in the United States exceeded collections by 7785 units (Block W: personal communication). If collections are restricted to the high-antibody titers and patient indications described in the article by Libster et al., the supply of convalescent plasma will be stressed. At my center, high-titer collections (as defined by the FDA) account for only 19.5% of seroreactive convalescent plasma donations. Shifting the pool of potential recipients away from those included in the EUA to the many infected outpatients whose risk of hospitalization and eventual need for advanced care cannot be precisely estimated should lead to the extension of convalescent plasma transfusions to prehospital venues (although this is not yet permitted in the EUA).

<u>Uncontrolled compassionate use of convalescent plasma in patients other than those with an early infection that is likely to progress to more severe illness should be discouraged</u>, even though clinicians recognize how difficult it can be to "just stand there" at the bedside of a patient in the ICU. Constraints on therapies for Covid-19 that are effective for limited patient populations are a powerful argument for continued consistent adherence to recommended nonpharmaceutical interventions and the rapid deployment and uptake of effective vaccines.

In an obfuscating way, Dr. Katz confirms that when high-dose COVID-19 Convalescent Plasma is given **EARLY**(<72 from time of onset or diagnosis) and is compared with placebo in age-matched patients ~70 years of age, progression to severe COVID-19 disease (e.g. pneumonitis, blood clots, etc.) is 16% versus 31%, respectively.

THUS, COVID-19 CONVALESCENT PLASMA when given <u>EARLY to</u> <u>an AGE COHESIVE GROUP</u> in the VIREMIC PHASE OF COVID-19 (<72 HOURS) has a 50% DECREASED / OBSERVED REDUCTION IN PROGRESSION to the LATER MULTIORGAN-SYSTEM PHASE

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

OF COVID-19 INVOLVING (1) THE CYTOKINE CASCADE STORM and (2) the ACCUMULATION OF DETRIMENTAL LEVELS OF BRADYKININ.

771) 2021-02-18 Whyte J: FDA revises EUA for COVID-19 Convalescent Plasma. WebMD. John Whyte, M.D., Chief Medical Officer at WebMD interviews Peter Marks, M.D., PhD, Director for the Center for Biologics Evaluation and Research at the U.S. FDA: FDA revises EUA for COVID-19 convalescent plasma. https://www.webmd.com/coronavirus-in-context/video/peter-marks-plasma

The following is a very important interview as Peter Marks, M.D., PhD as the Director for CBER at the FDA had the ability in March 2020 to have designated COVID-19 Convalescent Plasma a Biosimilar Biologic (like rabies vaccine, HyperTet, RhoGam, IVIG, etc.) and the designation of "Investigational" and all the Expanded Access / (compassionate use only) would have been avoided. This would have precluded the issuing of the eligibility criteria of March 24, 2020 which directed administration late in the course of the disease—THE WRONG TIME as is confirmed by Dr. Marks in the 2/18/2021 interview! Immediately following is from the March 24, 2021 FDA announcement. https://notifylibrary.org/sites/default/files/Investigational%20COVID-19%20Convalescent%20Plasma%20-%20Emergency%20INDs%20 %20FDA.pdf

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

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Eligible patients for use under expanded access provisions:

- o Must have laboratory confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - · respiratory failure,
 - septic shock, and/or

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convale... 2/3

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

- · multiple organ dysfunction or failure
- · Must provide informed consent

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

Start of the interview of Dr. Marks by Dr. Whyte:

JOHN WHYTE: Welcome, everyone. You're watching "Coronavirus in Context." I'm Dr. John Whyte, chief medical officer at WebMD. We're spending a lot of time talking about vaccines. But we can't forget about the role of therapeutics for those persons who have caught COVID and are having a serious case. And there's been some recent changes in when and how we should use convalescent plasma.

So to help explain these changes, I've asked Dr. Peter Marks. He's the director for the Center for Biologics Evaluation and Research at the US Food and Drug Administration. Welcome back, Dr. Marks.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

PETER MARKS: Thanks very much for having me.

JOHN WHYTE: Let's just take a minute and remind our audience—we have a lot of folks from Medscape, but also consumers—what is convalescent plasma?

PETER MARKS: So convalescent plasma is the blood plasma that's taken from an individual who has been infected with COVID-19 and who's recovered from the infection. In some cases, they might not even have known they had the infection, but they obviously did. And they might have antibodies that have been detected and told they had COVID-19, or they might have had a PCR test when they were sick with COVID, were told they had COVID-19, and afterwards, after they recover and they're fully recovered, they're eligible to potentially donate convalescent plasma, which is usually taken by plasmapheresis. People are put on a machine for about an hour, and the blood products taken out. And the blood cells are given back to the person. The plasma is taken off.

JOHN WHYTE: Now, the FDA authorized the use, under an emergency use authorization, of convalescent plasma in August of last year. And recently, you revised that authorization-- actually, in many ways made it more restrictive. Let's go over what the change in the EUA is.

PETER MARKS: Right. So the emergency use authorization that was issued in August was a very broad emergency use authorization, because at that time we were relying on the evidence at the time which said that it appeared that convalescent plasma could potentially benefit a broad swath of people. And we weren't really sure who it might benefit the absolute most. We knew it was best when given in high titer, and we knew that it seemed to be best in people who were treated earlier. But we couldn't rule out that it was having some benefit to people later on in the course of disease.

JOHN WHYTE: And at that time, they didn't have to be hospitalized.

PETER MARKS: We always required that the patients be hospitalized. It was always hospitalized patients. And what happened, then, is over the course of the past few months-- we follow the literature very closely-- there have been studies that have come out of various places. Some have been negative for convalescent plasma-- they said that it's not had a beneficial effect. Others have been quite positive.

And over the course of time, we've looked closely at them, and we sorted them out. And it became pretty clear that when people were treated early on with high-titer convalescent plasma, they seemed to be showing some benefit. And when you treat late, you just don't see that benefit. Particularly when you treat people who have been on a ventilator, it just-- with the rare exception of people who have defects in immunity, people who have diseases like hematologic malignancies like chronic lymphocytic leukemia-- those people, they may benefit late on, because they don't make antibodies.

But for the large majority of people who have normal immune systems, if you treat late, convalescent plasma is not seeming to benefit, whereas if you treat early, within the first few days after diagnosis, the data are increasingly supporting that there is some benefit there. It's not a massive benefit. It's a modest benefit.

JOHN WHYTE: How would you articulate that benefit?

PETER MARKS: I can cite the data that we have from roughly 20,000 individuals who received 1 unit of convalescent plasma. Roughly half of those people got high titer and half of them got low titer of various levels. And the people who got the higher-titer plasma had about a 2-percent absolute reduction in mortality at seven days, which translates into about a 15-percent relative reduction if they were not intubated.

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If they were intubated, they were on a ventilator, then there really wasn't any benefit. So those data really helped push us along towards saving it was time to kind of narrow down the emergency use authorization to say, look, don't use this late in people who are intubated-- that is, on a ventilator. Use it early on or earlier on in the course of disease.

Now, your next question might be, why not just use it as an outpatient? Hum. And the answer is-

JOHN WHYTE: Now you're interviewing yourself.

PETER MARKS: Nah. I might as well do that. I've done this enough. But the reason why we're not there yet is because we're waiting for some very well-designed studies that are being conducted, one by the National Heart, Lung, and Blood Institute, which will give us a good answer about the potential benefit in that setting.

JOHN WHYTE: Well, that's why I was asking you about hospitalized patients. Because if we talk about-- you mentioned it has to be used early on in the disease-- but what about severity of disease? Because many patients that aren't coming to the hospital until they're much further along-- so how do you do it, in the sense you want to do it early on, within those first couple of days, but sometimes we're telling patients not to come to the hospital or to the ER. So how do we balance that? So what's the severity of disease?

PETER MARKS: I think right now the way we balance it is we say that if you're somebody who's got early disease and you're interested, get onto the www.ClinicalTrials.gov and find one of the sites around you that might be doing outpatient clinical trials with convalescent plasma. There are a number of sites doing that.

But I think, otherwise, when people are admitted to the hospital, it's probably a good thing for physicians to think right away, is this somebody for whom convalescent plasma may make sense? Again, if someone's intubated in that first couple days, maybe not. On the other hand, <mark>if</mark> someone needs supplemental oxygen, those patients did seem to benefit.

JOHN WHYTE: Now, let's talk about the person's underlying immune response, their humoral immunity. So who are those patients? Many patients are often asking about, what if they're immunocompromised? What do they qualify for? Talk to our listeners about what's that patient population-- because that's a component, their underlying immunity function.

PETER MARKS: So it's a great question. And we've actually kept up with the case reports that have been coming out. They're not trials, but they're a case series that have come out from around the globe, and it's very convergent. If you treat people who don't make a sufficient amount of antibody, either because they have a primary immunodeficiency syndrome or because they have [INAUDIBLE] cancer, and they can't make them, if you treat them, even if you seem to treat those people late, they seem to have benefit.

And there are some amazing case reports-- obviously, it's always N-of-1-- case reports, you always have to take with a grain of salt-- but where people even very late on have had very good responses clearing viremia. So that kind of makes sense, right? Because if you're not able-- what we think, at least, that the antibodies are doing here-- the antibodies in convalescent plasma are acting like an antiviral, right? And if you give it early, they're acting like an antiviral would early on in getting things under control. Later on in the course of disease, where there are other organ damage effects, that's not the best time for an antiviral. And for those who are immunocompromised, it may be that they just have ongoing viremia, and you need to clear it. And giving them convalescent plasma helps take care of that.

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JOHN WHYTE: One question we have gotten asked, Dr. Marks, is for those patients who have been fully immunized, are they able to donate plasma?

PETER MARKS: So it's a great question. And it's one we're still debating. Right now, if people have not had COVID-19 and get immunized -- so they're people who are COVID-19-negative to start, then get immunized-- we're not considering them as convalescent plasma donors, because they're making antibodies against just the S protein that are in the current generation of mRNA vaccines that are authorized.

We don't know, in terms of the convalescent plasma response that we're seeing, how much of the benefit is from the S-protein antibodies versus N-protein antibodies or other antibodies that are there. And until we have a little better idea on that, we're a little hesitant to swing over to have vaccinated individuals donate.

But this is an absolutely great question, because we're very much looking into this now. It would be nice to understand, because soon we're going to have a large population of people who will be fully vaccinated, probably with high titers of S antibodies, and it would be nice to know this. So stay tuned. We do that for other infectious diseases, and maybe we'll see it coming for COVID-19 soon enough.

JOHN WHYTE: Tell us how staff are doing. You had your general work that you had to do, in terms of vaccines, other biologics. Now you have the whole issue of COVID. How is everyone managing it?

PETER MARKS: Well, I have to say, we are incredibly lucky at FDA. We have a staff that has risen to the occasion in an amazing way. They're keeping the normal freight moving. And while they're keeping the normal freight moving, they are taking care of the avalanche of COVID-19related applications.

Now, in some areas, there are a little lower number of applications than in others. But if you look, for instance, in the vaccine area, there is an avalanche there. And they're doing an incredible job keeping up. Same thing with, actually, some of the cellular therapies that have come in, and even the antibody therapies, et cetera. There are lots of them, right?

Our folks have done just an incredible job pitching in. People who have a little less work pitch in to those who are almost getting underwater in work. So it's been really wonderful. It has taken its toll. People are getting a little tired. And we're trying to make sure that we take care of people. But we're very lucky that people have really had such commitment to public health.

JOHN WHYTE: Absolutely. And then finally, all these emergency use authorizations that are happening across the agency-- do you expect sponsors to apply for full licensure in a few months?

PETER MARKS: Yeah. So I-- for the vaccine sponsors in particular, we've told them that if they want to come in for an EUA, they should expect-- it's actually in our guidance-- they should expect that they're going to come in for a biologics license application. And so that's why the work isn't going to end soon, because as we're now dealing with some of the emergency use authorizations where the vaccines are becoming more mature, they've been in use for a little bit, I would suspect in the not-toodistant future we may see their biologics license applications. And so there will be kind of a cohort that will come along of license applications in the coming months.

JOHN WHYTE: Well, Dr. Marks, I want to thank you for taking the time, the work that you and all the staff at the Center for Biologics Evaluation and Research and all of FDA are doing to keep us all safe.

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PETER MARKS: Thanks so much for having me today.

JOHN WHYTE: And if you have any questions about COVID, drop me a line. You can email us at drjohn@webmd.net as well as post it on Facebook, Twitter, and Instagram. Thanks for watching.

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- 775) 2021-02-24 Biden JR: Notice on the Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic. February 24, 2021 – Presidential Actions https://www.whitehouse.gov/briefing-room/presidential-actions/2021/02/24/noticeon-the-continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019covid-19-pandemic/
- 2021-02-25 Hinton DM: Emergency Use Authorization 094 regarding combination of bamlanivimab and etesevimab. (EUA led to the revocation of EUAs for bamlanivimab only). https://www.fda.gov/media/145801/download
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When severely ill with COVID-19, a person experiences two phases – an early phase dominated by the virus reproducing itself, which happens a lot in the lungs and leads to low oxygen levels; and a later phase where the body's immune system has a dangerous overreaction to the infection, which causes damage to other organs.

"The early phase, when the virus is really doing most of its reproduction and a lot damage, that's when we want to interfere with that reproduction. And that's what these antibodies do," said **Dr. Bruce Hall***, chief quality officer for BJC HealthCare.

That's why it's important to get tested at the first signs of illness and immediately contact a doctor, who must assess and refer patients for the infusion therapy, Hall said.

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The infusion takes about an hour, and patients are observed for another hour for any adverse reactions, the providers said. The centers are designed so infected patients do not share any space or entrances with other patients, some even requiring their own elevator.

Monoclonal antibody therapies for COVID-19 made by Eli Lilly and Regeneron were **approved** for emergency use by the FDA in November. To ensure access, the U.S. Department of Health and Human Services purchased over a million doses of the therapies and made them available to states at no cost. Doses are free of charge to patients.

The treatments have faced barriers to getting started, however, because of the time and logistics involved for the infusions.

Hospitals were swamped with caring for patients during the hardest-hit months of the pandemic and then tasked with setting up vaccinations. Many patients also may not know about the therapies or have the perceptions that they are only available to the well-connected, as they gained publicity when used by former President Donald Trump and other politicians. [e.g.: Trump, Carson, Christy, Giuliani, etc]

"It takes a little bit of effort to arrange and coordinate and manage the patients appropriately, but we think that it's all worth it if we can keep patients out of the hospital," said **Hall** with BJC, which has infusion centers at Christian Hospital in north St. Louis County, a Missouri Baptist Medical Center Clinic in Sunset Hills, Memorial Hospital in Belleville, Barnes-Jewish Hospital in St. Louis, and Boone Hospital Center in Columbia, Missouri.

Studies show that for every 15 people treated, one will be saved from needing to be hospitalized with COVID-19, **Hall** said. So far, the BJC locations are seeing similar results.

"That's probably a 30 to 40% reduction or more in terms of the risk of having to go into the hospital," he said. "For a disease that can be fatal, we are reducing that need to go into the hospital substantially."

* Bruce Hall, M.D., Ph.D., F.A.C.S., Professor of Surgery, Washington University School of Medicine (WUSOM). Through the VA-University Affiliation of 1946**, PL 79-293, both Dr. Hall and I are Attending Surgeons at the St. Louis (John Cochran) VAMC and Professors of Surgery from our respective universities: WUSOM and Saint Louis University School of Medicine (SLUSOM). Our desks are across the hall from each other on 5N of JCVAMC in A558, Unit I [WU] General Surgery and in A555, Unit II [SLU] General Surgery, respectively. Bruce's cell is: 314-401-0247 and my wife, Pam's cell is: 314-809-9634.

** U.S. Department of Veterans Affairs Research and Development: Milestones in VA-Academic Collaboration, https://www.research.va.gov/researchweek/press packet/Collaboration.pdf , December 2016.

https://www.bjc.org//Portals/0/Coronavirus/mAb-algorithm.pdf

BJC Monoclonal Antibody treatment for COVID-19 https://www.bjc.org/Coronavirus/mAb-for-COVID

778) 2021-02-25 BJC: Monoclonal antibody treatment for COVID-19. (first captured on the Way Back Machine 2/25/2021)

https://web.archive.org/web/20210225225153/https://www.bjc.org/Coronavirus/mAb-for-COVID-1 (Latest version: https://www.bjc.org/Coronavirus/mAb-for-COVID-1)

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- 779) 2021-02-26. U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210226104738/https://www.fda.gov/media/141480/download
- 780) 2021-02-26 Robbins R: The Biden administration buys 100,000 doses of a combination antibody treatment for high-risk Covid-19 patients. The New York Times, Feb 26, 2021. https://www.nytimes.com/2021/02/26/world/bamlanivimab-etesevimab-eli-lilly-monoclonal-antibodies.html
- 781) 2021-02-28 U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210228162844/https://www.fda.gov/media/141480/download
- 782) 2021-02-28 NIH-COVID-19 Treatment Guidelines, Convalescent Plasma, *Last Update: October 9, 2020.* February 28, 2021. https://web.archive.org/web/20210228150338/https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

[One will note, that even though the FDA had issued several EUAs, most significantly on February 4, 2021, the NIH continued its section on Convalescent Plasma after was based on the August 23, 2020 EUA announced by President Trump. The FDA Inclusion Criteria of only in Severe COVID-19 affected patients existed from March 24, 2020 until September 2, 2020. Most NIH registered prospective ClinicalTrials existing on September 2, 2020 were based on **That ERRONEOUS Inclusion Criteria**. Note that from October 9, 2020 to February 28, 2021, the NIH hedged its bets by including in the Convalescent Plasma last updated October 9, 2020: ...suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

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Convalescent Plasma

Last Updated: October 9, 2020

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.¹

Recommendation

 There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance. Despite meeting the "may be effective" criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population. Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing.

The Panel's assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents. 3,6,7

- 783) 2021-03-01 van Beusekom M: COVID meta-analysis: No benefit from convalescent plasma. CIDRAP, Center for Infectious Disease Research and Policy, University of Minnesota. https://www.cidrap.umn.edu/news-perspective/2021/03/covid-meta-analysis-no-benefit-convalescent-plasma
- 784) 2021-03-02 Hinton DM: Emergency Use Authorization 090 regarding Eli Lilly's bamlanivimab, March 2, 2021. (Now stamped REVOKED—revoked 4-16-2021) https://www.fda.gov/media/143602/download

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

785) 2021-03-02 NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms – Study shows the treatment safe, but provides no significant benefit in this group. U.S. National Institute of Health announcement is: https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescentplasma-emergency-department-patients-mild-symptoms

> The actual clinic trial, Convalescent Plasma in Outpatients with COVID-19 (SIREN C3PO) NCT04355767. was:

https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2 &rank=1

There are no reported results on the ClinicalTrials website of which the NIH is making its decision to halt the trial. The trial was underpowered where there was no stratification by age and the study was discontinued with recruitment of only half the number of planned patients. This study was run by: SIREN, Strategies to Innovate emeRgENcy Care Clinical Trials, https://clic-ctsa.org/node/9426.

NIH Announcement to discontinue the trial on March 2, 2021:

Launched in August 2020, the Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO(link is external)) was being conducted at 47 hospital emergency departments across the United States and had enrolled 511 of the 900 participant recruitment goal. It was specifically looking at the effectiveness of COVID-19 convalescent plasma - blood plasma derived from patients who have recovered from COVID-19 - in adults who came to an emergency department with mild to moderate symptoms they had for a week or less. These patients also had at least one risk factor associated with severe COVID-19, such as obesity, hypertension, diabetes, heart disease, or chronic lung disease, but none were ill enough at the time to be hospitalized.

(C3PO(link is external) https://siren.network/clinical-trials/c3po

C3PO Clinical Trial of COVID-19 **Convalescent Plasma of Outpatients**

Registered with ClinicalTrials.gov: NCT04355767

https://clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank

This is a registered NIH ClinicalTrials.gov Award Number: 10T2HL156812-01

Status: No new randomizations as of February 25, 2021.

NIH Press Release (March 2, 2021)

Media inquiries: Refer to Lenora Johnson, DrPH, MPH and Mark Sampson, and to this press release.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

The Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO) is a multi-center randomized, single blind, two arm, placebo controlled phase III trial with blinded outcome assessment to establish the safety and efficacy of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.

COVID-19 is a respiratory illness caused by the *Severe Acute Respiratory Syndrome Coronavirus* 2 (SARS-CoV-2). As of May 1, 2020, over 3 million persons worldwide have been diagnosed with COVID-19 and approximately 250,000 persons have died from this disease. The majority (80%) of cases are categorized as mild, while approximately 15-20% of cases are categorized as severe, with about 5% of all cases progressing into critical illness, characterized by hypoxemic respiratory failure, shock, and end-organ failure. Among the 5% who develop severe disease, as many as 50% die. At present there is no specific therapy for preventing the progression of COVID-19 from mild to severe disease.

Passive antibody therapy using plasma from donors who have been infected and then recovered (convalescent plasma, CP) contains neutralizing antibodies against the infectious agent. Specifically, CP has been used in different respiratory illness epidemics, including the 1918 influenza pandemic, the 2003 SARS-CoV-1 outbreak, and the 2009 H1N1 influenza pandemic. Use of CP for emerging infections has persisted because of strong mechanistic and observational data, but efficacy has yet to be well tested or demonstrated in clinical trials. At this moment, there is no high quality evidence to support the efficacy of CP for treating COVID-19 illness. Conceptually, CP has the highest chance of showing efficacy if used for early treatment of patients at the highest risk for severe disease and mortality.

The overarching goal of this trial is to confirm or refute the role of passive immunization as a safe and efficacious therapy in preventing the progression from mild to severe/critical COVID-19 illness and to understand the immunologic kinetics of anti-SARS-CoV-2 antibodies after passive immunization.

For more information on C3PO and convalescent plasma go to our <u>In the News</u> page. (https://siren.network/clinical-trials/c3po/in-the-news)

C3PO IN THE NEWS

March 10, 2021

 Convalescent Plasma Strikes Out As COVID-19 Treatment https://www.npr.org/975365309

October 22, 2020

 OHSU reserchers say they're having trouble recruiting patients for COVID-19 convalescent plasma trial

https://www.kptv.com/ohsu-researchers-say-theyre-having-trouble-recruiting-patients-for-covid-19-convalescent-plasma-trial/video 767f3558-10aa-5201-ad47-94322b60070d.html?block id=988363

September 8, 2020

 NIH clinical trial explores use of convalescent plasma in at-risk outpatients with early COVID-19

https://www.nhlbi.nih.gov/news/2020/nih-clinical-trial-explores-use-convalescent-plasma-risk-outpatients-early-covid-19

August 25, 2020

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

 UF Health enrolls first patients in national COVID-19 study on convalescent blood plasma

https://m.ufhealth.org/news/2020/uf-health-enrolls-first-patients-national-covid-19-study-convalescent-blood-plasma

August 19, 2020

New clinical trial at OHSU tests donated antibodies
 https://news.ohsu.edu/2020/08/18/new-clinical-trial-at-ohsu-tests-donated-antibodies

August 6, 2020

Will COVID-19 finally provide an answer on convalescent plasma?
 https://www.medpagetoday.com/infectiousdisease/covid19/87936

August 3, 2020

 UM and Other Michigan hospitals to treat COVID-19 patients with convalescent plasm.

https://www.michiganradio.org/post/um-and-other-michigan-hospitals-treat-covid-19-patients-convalescent-plasma

July 30, 2020

 Michigan hospitals test if plasma from recovering patients can curb COVID-19

https://www.bridgemi.com/michigan-health-watch/michigan-hospitals-test-if-plasma-recovering-patients-can-curb-covid-19

 Researchers at the University of Michigan's Michigan Medicine and three other medical centers were awarded a total of \$7 million from the National Heart, Lung, and Blood Institute (NHBLI) to study convalescent plasma in reducing symptoms of COVID-19 in patients with mild cases, Michigan Medicine announced Thursday.

https://www.clickondetroit.com/video/health/2020/07/30/michigan-medicine-7-million-in-funding-for-covid-19-therapy-trial/

 Michigan Medicine and three other medical centers receive \$7 million COVID-19 outpatient convalescent plasma therapy trial

https://www.uofmhealth.org/news/archive/202007/michigan-medicine-and-three-other-medical-centers-receive-

7?fbclid=lwAR2Rr1QbiOj6OxC0dcbv2Hw0Cn6uMlnx0BTz-buGJCf4SozAqutNDa6 1qo

 Trump urges people who who have recovered from COVID-19 to donate blood plasma

https://www.washingtonpost.com/health/2020/07/30/trump-urges-people-who-have-recovered-covid-19-donate-plasma/

https://www.c-span.org/video/?474383-1/president-trump-roundtable-discussion-donating-plasma

July 29, 2020

 UPMC studying whether convalescent plasma help coronavirus patients with mild symptoms

https://pittsburgh.cbslocal.com/2020/07/29/coronavirus-study-convalescent-plasma/

COVID-19 trial to study convalescent plasma in outpatient setting

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

https://web.musc.edu/about/news-center/2020/07/29/covid19-trial-to-studyconvalescent-plasma-in-outpatient-setting

March 10, 2021

Convalescent Plasma Strikes Out As COVID-19 Treatment https://www.npr.org/975365309

2021-03-10 Harris R: Convalescent plasma strikes out as COVID-19 Treatment. NPR, March 10, 2021, 5:01 AM ET

More than half a million Americans have received an experimental treatment for COVID-19 called convalescent plasma. But a year into the pandemic, it's not clear who, if anyone, benefits

That uncertainty highlights the challenges scientists have faced in their attempts to evaluate COVID-19 drugs.

On paper, treatment with convalescent plasma makes good sense. The idea is to take blood plasma from people who have recovered from COVID-19 and infuse it into patients with active infections. The antibodies in the donated plasma, in theory, would help fight the virus.

Based on that idea, last March Dr. Nicole Bouvier at the Icahn School of Medicine at Mount Sinai Hospital in New York decided to give it a try.

She recalls thinking, "we have this new disease that didn't have any known therapies, and convalescent plasma has been used in new epidemic and pandemic diseases," as recently as in an Ebola outbreak in West Africa a few years ago.

She says she was the first doctor to get special permission from the Food and Drug Administration to use it as an experimental treatment.

It was a huge commitment to line up people willing to donate plasma as well as to treat patients themselves, "so it was a big production," she says. "We ultimately screened over 70,000 people" and identified around 20,000 who had high antibody levels in their blood plasma.

Mount Sinai treated more than 1,400 patients, including throughout the height of New York City's nightmarish COVID-19 outbreak last spring. But all the while Bouvier had no idea whether the plasma really worked.

Finally, a couple of weeks ago, she had seen enough data from carefully controlled studies — and decided to stop offering the treatment.

"The straw that broke the camel's back was two very large cohort trials," she says. The RECOVERY Trial in the United Kingdom had studied more than 10,000 volunteers and found no benefit. Another one called CONCOR-1, run by Canadians, had studied nearly 1,000 patients. It, too, stopped recruiting new patients because doing so would have been futile. But those studies focused on people sick enough to be in the hospital. Dr. Arturo Casadevall at the Johns Hopkins Bloomberg School of Public Health is one of the prime advocates for convalescent plasma. He says he thinks the treatment needs to be done sooner, in the outpatient setting.

"From the very beginning here at Hopkins we set out to do outpatient trials," he says. "The trials were set up in March [of 2020], however it took many months to get the money to do it." With taxpayer money nowhere to be found, the study ultimately went forward with funding from the billionaire Michael Bloomberg, Casadevall says.

A year later, the study at Hopkins still doesn't have results. And it's not just a question of funding. The entire U.S. medical research system isn't set up to do what's needed to identify new treatments during a pandemic.

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Dr. Derek Angus, chair of critical care medicine at the University of Pittsburgh, says that in a public health emergency scientists should be able to evaluate new treatments at hundreds of hospitals, in a matter of months.

"People might roll their eyes and say that's impossible, but that's largely what the United Kingdom has done," Angus says. "For all our capacity in the United States, it's depressing that we can't do a U.S. version."

The U.K. was able to launch its vast study quickly because Britain has a national health system that not only provides treatment but can conduct research. Research in the U.S. is balkanized among universities, drug companies and funders.

"We pride ourselves on having a very federated, independent system," Angus says. "But, gosh, that is very hard to turn on a dime to solve national problems."

To give just one example, a national network of emergency room physicians got federal funding to treat people with convalescent plasma, in a study named C3PO. Their patients were sick enough to show up in the emergency room, but well enough to go home afterward.

"We should have been able to get this done as quickly as they did in the U.K.," says Dr. Kevin Schulman at Stanford University. "It was just a much slower process to set up."

Schulman at Stanford was responsible for some of the logistics. And they were a nightmare, he says.

"I said tongue in cheek at some point when we had five patients in our study that we had at least 500 people touch a paper for the five patients we had recruited. And that's the opposite in the UK." "Some of the contracts for the trial we are still negotiating even today," he adds. "You know, the U.K. didn't have any of that."

The C3PO study recently stopped recruiting patients. It had enrolled about 500 out of a planned 900, but an independent monitoring board concluded that continuing would have been futile. This further casts doubt on the value of convalescent plasma.

"I don't see any point in offering plasma outside a clinical trial," says Angus from Pitt.

Several trials are ongoing. And there's still a chance that some of them could identify a group of patients, treated at a particular time with a particular concentration of plasma, who would benefit. So Bouvier at Mount Sinai hasn't given up on it completely.

In retrospect, it's understandable why convalescent plasma doesn't help people hospitalized with significant illness, she says. Serious illness is caused primarily by the body's reaction. Respiratory viruses like these don't persist for long. "They're sort of like, 'wham, bam, thank you, ma'am.' And then they're gone," Bouvier says.

"If a study comes along that identifies a population in whom convalescent plasma is useful, we will use it in that population" she says.

And if it does appear to be helpful for people who are early in the course of disease, that raises another question: Would plasma be better than the monoclonal antibody drugs already authorized by the Food and Drug Administration for that purpose and easier to use?

Casadevall at Hopkins argues that plasma might be better, especially if new virus variants can evade the antibody drugs. Antibodies in the plasma of people who have recovered have apparently been successful in controlling whatever virus they encountered, so the treatment actually evolves along with the pandemic.

But to figure out whether convalescent plasma is better than monoclonal antibodies could require another large, time-consuming study in a research system not set up to be nimble.

You can contact NPR Science correspondent Richard Harris at rharris@npr.org.

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- 2021-03-04 United States Government / Mayo Clinic: Historical EAP program participation. [EAP=Expanded Access Program = Compassionate Use Program]. March 4, 2021. https://www.uscovidplasma.org/
- 787) 2021-03-05 Woodward A, DeAngelis A: A future COVID-19 vaccine could be squirted up the nose. The nasal spray could stop transmission, especially in kids. https://www.businessinsider.com/intranasal-covid-19-vaccine-spray-could-stem-spread-2021-3
- **788**) 2021-03-06-10 Levin J: Remdesivir versus standard of care for severe COVID-19. Conference on Retroviruses and Opportunistic Infections, Boston, MA, March 6-10, 2021. https://natap.org/2021/CROI/croi 197.htm
- **789**) 2021-03-6-10 Dougan M, Nirula A, Gottlieb RL, Azizad M, Mocherla B, Chen P, Huhn G, Adams AC, Schade AE, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM, for BLAZE-1 Investigators: Bamlanivimab+Eteseviman for treatment of COVID-19 in highrisk ambulatory patients. Conference on Retroviruses and Opportunistic Infections, Boston, MA, March 6-10, 2021. https://natap.org/2021/CROI/croi-71.htm

BLAZE-1 Phase 3: Summary

Phase 3 confirms and replicates Phase 2 findings, with 70% reduction in risk of hospitalization (p=0.0004), decreased viral load (p<0.001), and improved sustained symptom resolution (p=0.007)

Outcomes consistent with EUA for bamlanivimab alone (71% reduction in risk of hospitalization)

No death due to any cause (Placebo: 10 vs. bamlanivimab + etesevimab together: 0)

Clinically meaningful results reflect the potential of bamlanivimab and etesevimab together in offering strong protection to the most vulnerable patients

Results support the potential for neutralizing monoclonal antibody therapy to reduce mortality, burden on the health care system, and duration of symptomatic disease in infected high-risk individuals

2021-03-06 through 10 Mascolini M: Convalescent plasma has no effect on survival or disease course with severe COVID-19. Conference on Retroviruses and Opportunistic Infections, Boston, MA, March 6-10, 2021. https://natap.org/2021/CROI/croi 70.htm

> Convalescent plasma from people with COVID-19 did not prolong survival, improve disease course, or affect virologic or immunologic markers of people receiving the plasma during severe disease [1]. Results of this 87-person open-label randomized trial in the Netherlands suggested to the researchers that this therapy "should be studied as early as possible in the disease course or at least preceding the start of an autologous humoral response."

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791) 2021-03-06 through 10: (Reported by Jules Levin), Olender S, Walunas TL. Martinez E, Boffito M, Perez KK, Castagna A, Wang S, Goyal P, Ripamonti D, Bernardino JI, Haubrich RH, Chokkalingam AP, Wu G, Diaz-Cuervo H, Brainard D: Remdesivir versus standard of care for severe COVID-19. Conference on retroviruses and opportunistic infections. https://www.natap.org/2021/CROI/croi 197.htm

Background: Remdesivir (RDV), a direct-acting nucleotide pro-drug inhibitor of viral RNA-dependent RNA polymerases, was approved by the FDA for the treatment of hospitalized patients (pts) with COVID-19 infection and has been shown to shorten time to recovery and improve clinical outcomes in randomized clinical trials. We present the final Day 28 (D28) analysis of RDV vs standard of care (SOC) (interim Day 14 [D14] analysis published [Olender et al. Clin Infect Dis 2020]).

Methods: Final comparative analysis from two studies: a prospective phase 3, randomized study of RDV (RDV cohort) and a real-world retrospective cohort study of SOC (non-RDV cohort). Both studies enrolled pts with SARS-CoV-2 infection confirmed by polymerase chain reaction, who had oxygen saturation â‰□94% on room air or required supplemental oxygen and had pulmonary infiltrates. Pts in the RDV cohort were randomized 1:1 to receive IV RDV for 5 or 10 days (200 mg on Day 1 followed by 100 mg/day on Days 2–5 or 2–10), plus SOC; the two randomized dose-groups were combined for analysis. Pts in the non-RDV cohort received SOC as determined by local treatment practices (excluding RDV). Analysis populations were balanced using propensity score (PS) matching. The coprimary endpoints were D14 clinical recovery (determined using a 7-point ordinal scale) and D28 all-cause mortality. Factors associated with D28 mortality were assessed using a multivariable logistic regression model.

Results: After PS matching, baseline characteristics were generally similar in the RDV and non-RDV cohorts; median age 61 years, 63% male, 42% obese, 12% Black, 71% no/low-flow oxygen use, 25% high-flow oxygen, 3% ventilated. Pts in the RDV cohort had significantly higher D14 clinical recovery rates (65% vs 57%) and significantly lower D28 mortality rates (12% vs 16%) compared with the non-RDV cohort (Table). In the multivariable analysis, in addition to RDV use, a lower risk of death at D28 was associated with: younger age; being female; being White (versus being Black/African American); receiving an HIV protease inhibitor prior to baseline; not having cardiovascular disease or COPD; more days of symptoms prior to baseline; and being on room air or low-flow oxygen at baseline (versus being on invasive mechanical ventilation).

Conclusion: RDV was associated with significantly higher rates of clinical recovery at Day 14 and lower Day 28 mortality compared with SOC in hospitalized pts with severe SARS-CoV-2 infection.

Conclusions

- Remdesivir was associated with significantly higher rates of clinical recovery at Day 14 and lower Day 28 all-cause mortality compared with SOC treatment in hospitalized patients with severe COVID-19
- In the subgroup analysis, with limited sample sizes in some groups, a significant mortality benefit could be seen in patients on low-flow oxygen at baseline
- Overall, these data support the use of remdesivir treatment to improve clinical recovery and decrease mortality from severe COVID-19
- Findings are consistent with accumulating evidence supporting the use of remdesivir in patients with severe COVID-19¹⁻⁴
- Remdesivir may help to reduce the burden on hospitals during COVID-19 surges
- 792) 2021-03-08 Winn K: Blood center to phase out CCP donations—Due to strong inventory, decline in COVID-19 hospitalization rate, Blood Center will phase out COVID-19 Convalescent Plasma donations March 26, 2021.

https://www.bloodcenter.org/about/news/news-releases/blood-center-to-phase-out-ccp-donations/;

https://www.bloodcenter.org/webres/File/News%20Releases/CCP%20phase%20out%20March%202021/COVID19%20CCP%20phaseout_CICBC.pdf; and https://www.bloodcenter.org/hospitals/patient-services/convalescent-plasma/

793) 2021-03-09 Hinton DM: U.S. Food & Drug Administration Emergency Utilization Authorization (EUA) regarding COVID-19 Convalescent Plasma. https://www.fda.gov/media/141477/download

Following the August 23, 2020, authorization, additional studies, including randomized, controlled trials, have provided data to further inform the safety and efficacy of COVID-19 use. Based on assessment of these data, potential clinical benefit of transfusion of COVID-19 convalescent plasma in hospitalized patients with COVID-19 is associated with high titer units administered early in the course of disease. Transfusion of COVID-19 convalescent plasma in hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit. These considerations may be different in patients with suppressed or deficient humoral immunity.

⁶Based on what is known about the typical course of the illness and kinetics of the humoral immune response in COVID-19, for most hospitalized patients, early in the course of disease likely represents prior to respiratory failure requiring intubation and mechanical ventilation. The therapeutic window may be longer when CCP is administered to patients with clinical or laboratory evidence of impaired humoral immunity.

794) 2021-03-09 Karamyan VT: Review: Between two storms, vasoactive peptides or bradykinin underlie severity of COVID-19? Physiol Rep 2021 Mar 9; 9(5): e14796. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7941673/pdf/PHY2-9-e14796.pdf

Abstract

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a world-wide pandemic with overwhelming socioeconomic impact. Since inflammation is one of the major causes of COVID-19 complications, the associated molecular mechanisms have been the focus of many studies to better understand this disease and develop improved treatments for patients contracting SARS-CoV-2. Among these, strong emphasis has been placed on pro-inflammatory cytokines, associating severity of COVID-19 with so-called "cytokine storm." More recently, peptide bradykinin, its dysregulated signaling or "bradykinin storm," has emerged as a primary mechanism to explain COVID-19-related complications. Unfortunately, this important development may not fully capture the main molecular players that underlie the disease severity. To this end, in this focused review, several lines of evidence are provided to suggest that in addition to bradykinin, two closely related vasoactive peptides, substance P and neurotensin, are also likely to drive microvascular permeability and inflammation, and be responsible for development of COVID-19 pathology. Furthermore, based on published experimental observations, it is postulated that in addition to ACE and neprilysin, peptidase neurolysin (Nln) is also likely to contribute to accumulation of bradykinin, substance P and neurotensin, and progression of the disease. In conclusion, it is proposed that "vasoactive peptide storm" may underlie severity of COVID-19 and that simultaneous inhibition of all three peptidergic systems could be therapeutically more advantageous rather than modulation of any single mechanism alone.

- 795) 2021-03-10 Association of American Blood Banks (AABB): Regulatory update: FDA Revises CCP EUA, Adds Abbott test. https://www.aabb.org/news-resources/news/article/2021/03/10/regulatory-update-fda-revises-ccp-eua-adds-roche-test
- 796) 2021-03-18 Juneja K, Humeniuk R, Porter D, Cao H, Feng J: Reply to Yan and Muler, "Remdesivir for COVID-19: Why not dose higher?" Antimicrobial Agents and Chemotherapy, 2021 April; 65(4): e1-e3. https://aac.asm.org/content/aac/65/4/e00085-21.full.pdf
- 797) 2021-03-18 Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiffins CC, Bruno KA, Klompas AM, Lesseer ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, Verdun NC, Marks P, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather DL: Wright RS, Casadevall A: Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021 Mar 18; 384 (11): https://www.nejm.org/doi/full/10.1056/nejmoa2031893 and https://www.nejm.org/doi/pdf/10.1056/NEJMoa2031893?articleTools=true

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

M.J. Joyner, R.E. Carter, J.W. Senefeld, S.A. Klassen, J.R. Mills, P.W. Johnson, B.S. Theel, C.C. Wiggins, K.A. Bruno, A.M. Klompas, E.R. Lesser, K.L. Kurze, M.A. Sexton, J.C. Diaz Soto, S.E. Baker, J.R.A. Shepherd, N. van Helmond, N.C. Verdun, P. Marks, C.M. van Buskirk, J.L. Winters, J.R. Stubbs, R.F. Rea, D.O. Hodge, V. Herasevich, E.R. Whelan, A.J. Clayburn, K.F. Larson, J.G. Ripoll, K.J. Andersen, M.R. Buras, M.N.P. Vogt, J.J. Dennis, R.J. Regimbal, P.R. Bauer J.E. Blair, N.S. Paneth, D.L. Fairweather, R.S. Wright, and A. Casadevall

ABSTRACT

Convalescent plasma has been widely used to treat coronavirus disease 2019 (Covid-19)

under the presumption that such plasma contains potentially therapeutic antibodies

to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can be passively transferred to the plasma recipient. Whether convalescent plasma with high

antibody levels rather than low antibody levels is associated with a lower risk of

death is unknown. death is unknown.

In a retrospective study based on a U.S. national registry, we determined the anti-SARS-CoV-2 IgG antibody levels in convalescent plasma used to treat hospitalized adults with Covid-19. The primary outcome was death within 30 days after plasma transfusion. Patients who were enrolled through July 4, 2020, and for whom data on anti-SARS-CoV-2 antibody levels in plasma transfusions and on 30-day mortality were available were included in the analysis.

Of the 3082 patients included in this analysis, death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group. The association of anti-SARS-CoV-2 antibody levels with the risk of death from Covid-19 was moderated by mechanical ventilation status. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before observed among patients who had not received mentalities withinston below transfusion (relative risk, 0.66; 95% confidence interval [CI], 0.48 to 0.91), and no effect on the risk of death was observed among patients who had received mechanical ventilation (relative risk, 1.02; 95% CI, 0.78 to 1.32).

Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the Department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.)

Drs. Joyner, Carter, and Senefeld and Drs Paneth, Fairweather, Wright, and Casa-devall contributed equally to this article. This article was published on January 13, 2021, at NEJM.org.

N Engl J Med 2021;384:1015-27.
DOI: 10.1056/NEJMoa2031893
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- 2021-03-23 FDA: Expanded access. https://www.fda.gov/news-events/public-healthfocus/expanded-access
- 2021-03-26 Gupta S: Autopsy of a pandemic: 6 doctors at the center of the US Covid-19 response. CNN health. https://www.cnn.com/2021/03/26/health/covid-war-doctors-sanjaygupta/index.html
- 2021-03-29 Centers for Disease Control and Prevention: CDC real-world study confirms protective benefits of mRNA COVID-19 Vaccines—Study involved health care personnel, firs responders, and essential workers in six states. https://www.cdc.gov/media/releases/2021/p0329-COVID-19-Vaccines.html
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8006883/pdf/5 2021 Article 612.pdf

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- **803)** 2021-03-29 Collinson S: America's pandemic dead deserve accountability after Birx disclosure. CNN politics. https://www.cnn.com/2021/03/29/politics/coronavirus-deborah-birx-donald-trump-joe-biden/index.html
- **804)** 2021-03-29 Howard J: "All the doctors" working on US coronavirus response received death threats, Birx says. CNN Health. https://www.cnn.com/health/live-news/covid-pandemic-doctors-cnn-special/h c99768531e3b8232888d7684b37b539f
- 805) 2021-03-30. U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210330024720/https://www.fda.gov/media/141480/download
- 806) 2021-03-31 Hinton DM: QuickVue At-Home OTC COVID-19 Test EUA210269 https://www.fda.gov/media/147247/download
- 807) 2021-04 CDC: Clinical considerations: Myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults. CDC, Vaccines & Immunizations. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html
- **808)** 2021-04 Spellberg B, Nielsen TB, Casadevall A: Antibodies, Immunity, and COVID-19. JAMA Internal Medicine 2021 April; 181 (4): 460-462. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2773575

In summary, a robust and well-designed seroprevalence study using residual serum samples from across the US has found that herd immunity to SARS-Cov-2 is nowhere in sight, even as the COVID-19 pandemic has raged on for a year. The good news is that the limited number of reinfections of SARSCoV-2 to date, and the experience with natural infections with other viruses, suggests that protective immunity to COVID-19 should result, a harbinger for the success of vaccines. The bad news is that, like the 1918 influenza pandemic, achieving herd immunity through natural infections will take years of painful sacrifice that are tallied in numerous deaths, severe longterm health sequelae, and widespread economic disruption and hardship. Let us hope that safe and effective vaccines help avoid the consequences of naturally developing herd immunity toCOVID-19, as they have reliably done for so many other respiratory viruses.

809) 2021-04-02 Center for Constitutional Rights: Factsheet: U.S. Sanctions on the International Criminal Court. https://ccrjustice.org/factsheet-us-sanctions-international-criminal-court

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals Prevention: Active Immunization: Vaccines

- 2021-04-06 Liew OW, Ling SSM, Lilyanna S, Zhou Y, Wang IP, Chong JPC, NG YX, Lim AES, Leong ERY, Lin Q, Lim TK, Lin FQ, Ng EMW, Ng TW, Richards AM: Epitopedirected monoclonal antibody production using a mixed antigen cocktail facilitates antibody characterization and validation. Nature communications biology 2021; 4 (Article number 441): 1-17. https://www.nature.com/articles/s42003-021-01965-x Author correction published 04 May 2021.
- 2021-04-08 NIH COVID-19 Treatment Guidelines. The COVID-19 Treatment Guidelines Panel's statement on the Emergency Use Authorization of Anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19. (This is copied verbatim as it is so important)

http://web.archive.org/web/20210417040352/https://www.covid19treatmentguidelines.nih.go v/statement-on-anti-sars-cov-2-monoclonal-antibodies-eua/

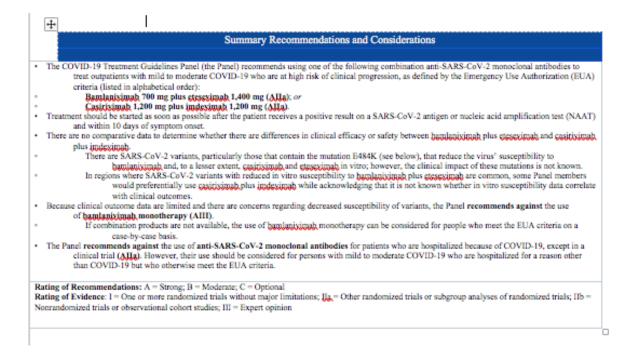
The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

Last Updated: April 8, 2021

Anti-SARS-CoV-2 monoclonal antibodies that target the SARS-CoV-2 spike protein and block virus entry into cells have been evaluated for the treatment of COVID-19. To date, the Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for the following anti-SARS-CoV-2 monoclonal antibodies and combinations: bamlanivimab alone, bamlanivimab plus etesevimab, and casirivimab plus imdevimab.

Data are emerging on the currently available anti-SARS-CoV-2 monoclonal antibodies, including preliminary data from a Phase 3 trial of casirivimab plus imdevimab, and on the in vitro susceptibility of SARS-CoV-2 variants to anti-SARS-CoV-2 monoclonal antibodies. After reviewing the available data, the COVID-19 Treatment Guidelines Panel (the Panel) has updated its recommendations on the use of anti-SARS-CoV-2 monoclonal antibodies in outpatients with mild to moderate COVID-19 who are at high risk of disease progression. In addition, the Panel notes that, because of an increasing number of reports of variants that are resistant to bamlanivimab alone, this product will no longer be distributed by the U.S. government.1.

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SARS-CoV-2 Variants of Concern or Interest and Their Susceptibility to Anti-SARS-CoV-2 **Monoclonal Antibodies**

In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab and may have lower sensitivity to etesevimab and casirivimab. However, the impact of these mutations on the clinical response to antibody combinations is uncertain, and the prevalence of these variants in different regions may vary.² Of note:

- The B.1.1.7 variant of concern, which is increasing in frequency in the United States, retains in vitro susceptibility to the anti-SARS-CoV-2 monoclonal antibodies that are currently available through EUAs.³⁻⁵
- The B.1.351 variant of concern has been infrequently detected among the SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.^{4,6,7} In vitro studies suggest that bamlanivimab plus etesevimab has markedly reduced activity against the B.1.351 variant.³ In vitro studies also suggest that the K417N mutation, which is present in this variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵
- The P.1 variant of concern has been infrequently detected among the SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.^{3,7} In vitro studies suggest that bamlanivimab plus etesevimab also has markedly reduced activity against the P.1 variant.^{3,6,8} In vitro studies also suggest that the K417T mutation, which is present in this variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵
- The B.1.429/B.1.427 variants of concern (also called 20C/CAL.20C) that are circulating in parts of the United States, including California, Arizona, and Nevada, have the L452R mutation. This mutation is associated with a marked reduction in in vitro susceptibility to bamlanivimab. There appears to be a modest in vitro decrease in susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.³

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• The B.1.526 variant of interest is circulating in parts of the United States, such as New York. It commonly has the E484K mutation, which is associated with a marked reduction in in vitro susceptibility to bamlanivimab.3 There appears to also be reduced in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.3 In vitro studies suggest that the E484K mutation may reduce casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵

Ongoing <u>population-based genomic surveillance</u> of the types and frequencies of circulating SARS-CoV-2 variants and studies on the susceptibility of different variants to available anti-SARS-CoV-2 monoclonal antibodies will be important in defining the utility of specific monoclonal antibodies in the future.

Rationale for Recommending Bamlanivimab Plus Etesevimab

In the Phase 3 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, all the participants met the criteria for being at high risk for progressing to severe COVID-19 and/or hospitalization (as defined in the EUA). A total of 1,035 participants were randomized to receive bamlanivimab 2,800 mg plus etesevimab 2,800 mg (n = 518) or placebo (n = 517). The median participant age at baseline was 56 years; 31% of the participants were aged ≥65 years. Across the arms, 52% of the participants were women, 87% were White, 29% were Hispanic/Latinx, and 8% were Black or African American. The mean duration of symptoms at study enrollment was 4 days, and 77% of the participants had mild COVID-19.

The primary endpoint was the proportion of participants who had a COVID-19-related hospitalization (defined as \ge 24 hours of acute care) or who died from any cause by Day 29. Endpoint events occurred in 11 of 518 participants (2%) in the bamlanivimab plus etesevimab arm and in 36 of 517 participants (7%) in the placebo arm. Compared to the placebo-treated participants, the participants who received bamlanivimab plus etesevimab had a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death from any cause (P < 0.001). There were no deaths in the bamlanivimab plus etesevimab arm, and 10 deaths occurred in the placebo arm (10 of 517 participants [2%] died; P < 0.001).

Secondary virologic endpoints included SARS-CoV-2 levels on nasopharyngeal (NP) swab assays at different time points. Study participants who received bamlanivimab plus etesevimab had a greater and more rapid decline in virus levels than those who received placebo. The proportion of participants with persistently high viral loads (defined as a SARS-CoV-2 level >5.27 log10 copies/mL at Day 7) was 10% in the bamlanivimab plus etesevimab arm and 29% in the placebo arm (P < 0.000001).

Recommendations for the use of bamlanivimab plus etesevimab should be considered in the context of the following limitations:

- The doses authorized in the EUA are bamlanivimab 700 mg plus etesevimab 1,400 mg, which are different from the doses of bamlanivimab 2,800 mg plus etesevimab 2,800 mg used in the Phase 3 BLAZE-1 study. The lower dose was authorized by the FDA based on preliminary data from BLAZE-4, a double-blind, placebo-controlled, randomized Phase 2 trial.³ The available data demonstrate that the antiviral activity of bamlanivimab 700 mg plus etesevimab 1,400 mg is similar to that of bamlanivimab 2,800 mg plus etesevimab 2,800 mg.
- The results of the Phase 3 BLAZE-1 trial have not been peer reviewed and published.
- The Panel's recommendations are based on preliminary results only, and the details on the study design, follow-up, and methods are currently limited. When peer-reviewed data for the Phase 3 BLAZE-1 trial become publicly available, the Panel will review the results and update the recommendations if necessary.

Rationale for Recommending Casirivimab Plus Imdevimab

The updated recommendation for the use of casirivimab plus imdevimab is based on Phase 3 results from the R10933-10987-COV-2067 study (the information from this study is currently available only in a press

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release, and there is currently no peer-reviewed preprint or publication). 9,10 This trial compared 1,355 participants who received casirivimab 1,200 mg plus imdevimab 1,200 mg to 1,341 participants who received placebo.

The modified full analysis set (mFAS) included participants who had a positive SARS-CoV-2 polymerase chain reaction result from an NP swab at randomization and one or more risk factors for severe COVID-19. In the mFAS cohort:

- The median participant age at baseline was 50 years. Across the arms, 35% of the participants were Hispanic/Latinx and 5% were Black or African American. The median duration of symptoms prior to enrollment was 3 days.
- COVID-19-related hospitalizations or death from any cause were reported in 18 of 1,355 participants (1.3%) in the casirivimab plus imdevimab arm and 62 of 1,341 participants (4.6%) in the placebo arm (P < 0.0001). This represents a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death in the casirivimab plus imdevimab treatment participants.
- In the full analysis set, there was 1 death out of 1,849 participants in the casirivimab plus imdevimab arm and 5 deaths out of 1,843 participants in the placebo arm.

Recommendations for casirivimab plus imdevimab should be considered in the context of the following limitations:

- The results of this clinical trial have not been peer reviewed and published.
- The Panel's recommendation is based on preliminary results only, and the details on the study design, follow-up, and methods are limited. When peer-reviewed data for this trial become publicly available, the Panel will review the results and update the recommendations if necessary.

Rationale for Recommending Against the Use of Bamlanivimab Monotherapy

As noted above, several circulating SARS-CoV-2 variants have mutations that are associated with reduced in vitro susceptibility to certain anti-SARS-CoV-2 monoclonal antibodies that are available through EUAs. In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab alone and possibly lower sensitivity to etesevimab and casirivimab. Reduced in vitro susceptibility to both antibodies in a combination regimen is currently uncommon. Because this field is moving quickly, and real-time testing for variants and mutations is not currently available, it seems prudent to use therapeutic options for which reduced susceptibility to the entire regimen is less likely. Therefore, the Panel recommends against the use of bamlanivimab monotherapy (AIII). If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.

Rationale for Recommending Against the Use of Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Who Are Hospitalized for COVID-19

The FDA EUAs do not authorize the use of these antibodies in patients who are hospitalized for COVID-19, although their use could be considered for patients who are hospitalized for a non-COVID-19 indication and who meet the EUA criteria for the use of these products. See Anti-SARS-CoV-2 Monoclonal Antibodies for further discussion of the clinical trial data for hospitalized patients.

Anti-SARS-CoV-2 monoclonal antibodies may be available through expanded access programs for the treatment of immunocompromised patients who are hospitalized because of COVID-19. It is not vet known whether these antibodies provide clinical benefits in people with B-cell immunodeficiency or other immunodeficiencies.

Vaccination

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

SARS-CoV-2 vaccination should be deferred for at least 90 days in people who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses.¹¹

For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.¹¹

High-Risk Criteria in the Emergency Use Authorizations for Anti-SARS-CoV-2 Monoclonal Antibodies

The FDA EUAs for all available anti-SARS-CoV-2 monoclonal antibodies and combinations have the same criteria for use: they allow for the use of the monoclonal antibodies for the treatment of COVID-19 in nonhospitalized adults and children aged ≥12 years and weighing ≥40 kg who are at high risk for progressing to severe COVID-19 and/or hospitalization.³

High-risk individuals as specified in the EUA are those who meet at least one of the following criteria:

- Body mass index (BMI) ≥35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥65 years
- Aged ≥55 years and have:
- Cardiovascular disease; or
- Hypertension; or
- Chronic obstructive pulmonary disease/other chronic respiratory disease.
- Aged 12 to 17 years and have:
- BMI ≥85th percentile for their age and gender based on the <u>Centers for Disease Control and Prevention</u> growth charts; *or*
- Sickle cell disease; or
- Congenital or acquired heart disease; or
- Neurodevelopmental disorders (e.g., cerebral palsy); or
- A medically related technological dependence that is not related to COVID-19 (e.g., tracheostomy, gastrostomy, positive pressure ventilation); *or*
- Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.
- 811) 2021-04-12 Regeneron: Phase 3 prevention trial showed 81% reduced risk of symptomatic SARS-COV-2 infections with subcutaneous administration of REGEN-COV[™] (Casirivimab with imdevimab) <a href="https://investor.regeneron.com/news-releases/news-release-details/phase-3-prevention-trial-showed-81-reduced-risk-symptomatic-sars#:~:text=00%20AM%20EDT-_news-releases/news-releas
- 812) 2021-04-12 Regeneron: Phase 3 Prevention Trial Showed 81% Reduced Risk of Symptomatic SARS-CoV-2 Infections with Subcutaneous Administration of REGEN-COVTM (casirivimab with imdevimab). https://investor.regeneron.com/node/25016/pdf

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PHASE 3 PREVENTION TRIAL SHOWED 81% REDUCED RISK OF SYMPTOMATIC SARS-COV-2 INFECTIONS WITH SUBCUTANEOUS ADMINISTRATION OF REGEN-

COVTM (CASIRIVIMAB WITH IMDEVIMAB) TARRYTOWN, N.Y., April 12, 2021 /PRNewswire/ --

REGEN-COV rapidly protected household contacts from exposure to SARS-CoV-2 at home, with 72% protection against symptomatic infections in the first week, and 93% in subsequent weeks

Among individuals who developed symptomatic infections, REGEN-COV recipients cleared the virus faster and had much shorter symptom duration

Regeneron will share data with U.S. FDA and request EUA expansion to include COVID prevention for appropriate populations, using a 1,200 mg subcutaneous dose

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive results from a Phase 3 trial (2069A) assessing the ability of REGEN-COVTM (casirivimab with imdevimab) to reduce the risk and burden of COVID-19 infection among household contacts of SARS-CoV-2 infected individuals. The trial, which was jointly run with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), met its primary and key secondary endpoints, showing that REGEN-COV 1,200 mg administered subcutaneously (SC) reduced the risk of symptomatic infections by 81% in those who were not infected when they entered the trial.

"These data suggest that REGEN-COV can complement widespread vaccination strategies, particularly for those at high risk of infection. Importantly, to date REGEN-COV has been shown in vitro to retain its potency against emerging COVID-19 variants of concern," said Myron Cohen, M.D., who leads the monoclonal antibody efforts for the NIH-sponsored COVID Prevention Network (CoVPN) and is Director of the Institute for Global Health & Infectious Diseases at the University of North Carolina at Chapel Hill. "Despite standard precautions to reduce transmission, nearly 10% of unvaccinated individuals living with an infected person developed symptomatic infections if they did not receive REGEN-COV. If authorized, convenient subcutaneous administration of REGEN-COV could help control outbreaks in high-risk settings where individuals have not yet been vaccinated, including individual households and group living settings."

The Phase 3, double-blind, placebo-controlled trial assessed the effect of REGEN-COV on uninfected individuals without anti-SARS-CoV-2 antibodies or any COVID-19 symptoms, who lived in the same household as an individual who tested positive for SARS-CoV-2 within the prior 4 days. The trial enrolled 1,505 people who were not infected with SARS-CoV-2 at baseline and randomized to receive either 1 dose of REGEN-COV (1,200 mg) or placebo, administered as SC injections.

"These findings are very encouraging and suggest that REGEN-COV is highly effective at preventing symptomatic COVID-19 in household contacts of SARS-CoV-2 infected individuals," said Dan H. Barouch, M.D., Ph.D., co-principal investigator of the trial and Director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center and Professor of Medicine at Harvard Medical School. "The rapid and robust protection, together with the subcutaneous route of administration, support the practical utility of these antibodies in protecting

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against COVID-19 in multiple settings, including after high-risk exposures. These antibodies may be particularly useful in individuals who are not yet vaccinated, and may also have potential in those who are immunosuppressed and may not respond well to vaccines."

On average, individuals treated with REGEN-COV who experienced a symptomatic infection resolved their symptoms in 1 week, compared to 3 weeks with placebo. Infected individuals also cleared the virus faster with REGEN-COV.

"With more than 60,000 Americans continuing to be diagnosed with COVID-19 every day, the REGEN-COV antibody cocktail may help provide immediate protection to unvaccinated people who are exposed to the virus, and we are also working to understand its potential to provide ongoing protection for immunocompromised patients who may not respond well to vaccines," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "We thank the individuals, investigators and our collaborators involved in the trial, and look forward to rapidly discussing these results with regulatory authorities."

- 813) 2021-04-12 Regeneron: Phase 3 Prevention Trial Showed 81% Reduced Risk of Symptomatic SARS-CoV-2 Infections with Subcutaneous Administration of REGEN-COVTM (casirivimab with imdevimab). https://investor.regeneron.com/node/25016/pdf
- 814) 2021-04-13 Parkins K: Regeneron's antibody cocktail helps prevent and treat COVID-19 in Phase III studies. https://www.clinicaltrialsarena.com/news/regenerons-antibody-cocktail-regen-cov-helps-prevent-and-treat-covid-19-in-phase-3-studies/
- 815) 2021-04-14: Dutta SS: Early monoclonal antibody therapies beneficial for COVID-19, finds study. News Medical Life Sciences. Apr 14, 2021. https://www.news-medical.net/news/20210414/Early-monoclonal-antibody-therapies-beneficial-for-COVID-19-finds-study.aspx

A team of scientists recently conducted a large-scale study at Northwell Health, New York, USA, to evaluate the efficacy of neutralizing monoclonal antibody (MAB) therapies in preventing disease progression among patients with mild to moderate coronavirus disease 2019 (COVID-19). The findings reveal that the timing of initiating MAB therapy is a crucial factor in determining its efficacy against COVID-19. The study is currently available on the <u>medRxiv</u>* preprint server.

The medRxiv* preprint server is as follows: Jarrett M, Licht WB, Bock K, Brown Z, Hirsch JS, Coppa K, Brar R, Bello S, Nash IS: Early experience with neutralizing monoclonal antibody therapy for COVID-19. https://www.medrxiv.org/content/10.1101/2021.04.09.21255219v1.full.pdf

- **816)** 2021-04-14 AABB: Toolkit update 04/14/2021COFVID-19 Convalescent Plasma under emergency use authorization. https://www.aabb.org/docs/default-source/default-document-library/regulatory/toolkit-for-ccp-under-eua.pdf?sfvrsn=741be857">https://www.aabb.org/docs/default-source/default-document-library/regulatory/toolkit-for-ccp-under-eua.pdf?sfvrsn=741be857">https://www.aabb.org/docs/default-source/default-document-library/regulatory/toolkit-for-ccp-under-eua.pdf?sfvrsn=741be857 18
- **817)** 2021-04-14 Kummer L: Monoclonal antibodies can cut risk of hospitalization, death by 70% in COVID-19 patients. FOX 17, West Michigan.

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https://www.fox17online.com/news/local-news/kzoo-bc/kalamazoo/monoclonal-antibodies-can-cut-risk-of-hospitalization-death-by-70-in-covid-19-patients

- 818) 2021-04-16 Linnane C: Eli Lilly asks FDA to revoke EUA for COVID-19 antibody treatment alone to speed transition to combination therapy. April 16, 2021. https://www.marketwatch.com/story/eli-lilly-asks-fda-to-revoke-eua-for-covid-antibody-treatment-alone-to-speed-transition-to-combination-therapy-2021-04-16
- **819)** 2021-04-16. Hinton DM: Revocation the EUA for the investigational monoclonal antibody therapy bamlanivimab, *when administered alone*... https://www.fda.gov/media/147629/download
- **820)** 2021-04-16. FDA: FDA News release: Coronavirus (COVID-19) Update: FDA revokes Emergency Use Authorization for monoclonal antibody Bamlanivimab. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab
- 821) 2021-04-17 Thomas K, Weiland N: The Covid-19 Plasma boom is over. What did we learn from it? *The New York Times* https://www.nytimes.com/2021/04/17/health/covid-convalescent-plasma.html finance.yahoo.com/news/2020-04-21 <a href="https://finance.yahoo.com/news/covid-19-plasma-boom-over-183252295.html?guccounter=1&guce_referrer=aHR0cHM6Ly93d3cuZ29vZ2xlLmNvbS8&guce_referrer_sig=AQAAANsdGj4POGFCOwCCvZ4XWhRaSO6gMHERUyo72az7g290KE2n3pfeL_FY2CdR6-UUXduMuGrujDf64hDPbHQ8FRjIAjEYSxQ5OratcmUofgoxaRiPA3c2ci2KFC6b9YDVJE7BqZPF_J0ff14Ften5FlbG400-F-ASWAgroYWYEv7p

The Trump administration, buoyed by proponents at elite medical institutions, seized on plasma as a good-news story at a time when there weren't many others. It awarded more than \$800 million to entities involved in its collection and administration, and put Dr. Anthony S. Fauci's face on billboards promoting the treatment.

But by the end of the year, good evidence for convalescent plasma had not materialized, prompting many prestigious medical centers to quietly abandon it. By February, with cases and hospitalizations dropping, demand dipped below what blood banks had stockpiled. In March, the New York Blood Center called Mr. Cohen to cancel his 12th appointment. It didn't need any more plasma.

A year ago, when Americans were dying of Covid at an alarming rate, the federal government made a big bet on plasma. No one knew if the treatment would work, but it seemed biologically plausible and safe, and there wasn't much else to try. All told, more than 722,000 units of plasma were distributed to hospitals thanks to the federal program, which ends this month.

Because the government gave plasma to so many patients outside of a controlled clinical trial, it took a long time to measure its effectiveness. Eventually, studies did emerge to suggest that under the right conditions, plasma might help. But enough evidence has now accumulated to show that the country's broad, costly plasma campaign had little effect, especially in people whose disease was advanced enough to land them in the hospital.

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In interviews, three federal health officials — Dr. Stephen M. Hahn, the former commissioner of the Food and Drug Administration; Dr. Peter Marks, a top F.D.A. regulator; and Dr. H. Clifford Lane, a clinical director at the National Institutes of Health — acknowledged that the evidence for plasma was limited.

"The data are just not that strong, and it makes it makes it hard, I think, to be enthusiastic about seeing it continue to be used," Dr. Lane said. The N.I.H. recently halted an outpatient trial of plasma because of a lack of benefit.

- 822) 2021-04-18 U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://web.archive.org/web/20210418170456/https://www.fda.gov/media/141480/download
- 823) 2021-04-19 U.S. Food & Drug Administration: Clinical Memorandum, EUA 26382, COVID-19 Convalescent Plasma. https://www.fda.gov/media/141480/download
- 824) 2021-04-21 NIH COVID-19 Treatment Guidelines: Convalescent Plasma. Last Updated: April 21, 2021. https://www.covid19treatmentguidelines.nih.gov/therapies/antisars-cov-2-antibody-products/convalescent-plasma/

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of low-titer COVID-19 convalescent plasma for the treatment of COVID-19 (AIIb).
 - Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.

For Hospitalized Patients With COVID-19 Who Do Not Have Impaired Immunity

- The Panel recommends against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in mechanically ventilated patients (AI).
- The Panel recommends against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial (AI).

For Hospitalized Patients With COVID-19 Who Have Impaired Immunity

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.
 - Observational data including data from case reports, case series, and a retrospective case control study suggest a benefit of COVID-19 convalescent plasma in patients with various primary and secondary humoral immunodeficiencies.²⁻¹⁶
 - Several case reports indicate that patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with COVID-19 convalescent plasma. 17-19
 - High-titer convalescent plasma is authorized under the EUA for the treatment of hospitalized patients with COVID-19 and impaired immunity.

For Nonhospitalized Patients With COVID-19

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There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalized, except in a clinical trial.

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- Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.
- Results from additional adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of COVID-19 convalescent plasma in the treatment of nonhospitalized patients with COVID-19
- **825)** 2021-04-22 CDC: The Tuskegee Timeline. Last reviewed April 22, 2021. https://www.cdc.gov/tuskegee/timeline.htm
- 826) 2021-04-23 NIH COVID-19 Treatment Guidelines (First copy that eliminated Convalescent Plasma *Last updated October 9, 2020* completely as a therapeutic option.) https://web.archive.org/web/20210424024531/https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf
- 827) 2021-04-25 Auwaerter PG: Coronavirus COVID-19 (SARS-CoV-2). Johns Hopkins ABX Guide, Johns Hopkins Medicine POC-IT Guides.

 https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19_SARS_CoV_2
- **828)** 2021-04-25 Prior R: Blood banks phase out collecting convalescent plasma, but fear a US blood shortage. 58 WDJT Milwaukee. https://www.cbs58.com/news/blood-banks-phase-out-collecting-convalescent-plasma-but-fear-a-us-blood-shortage
- **829)** 2021-04-27 U.S. Treasury Data Lab: How is the federal government funding relief efforts for COVID-19? https://datalab.usaspending.gov/federal-covid-funding/
- 830) 2021-04-30 CDC & IDSA: Monoclonal antibodies. COVID-19 Real-time Learning Network. (Last update) https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/monoclonal-antibodies/
- 831) 2021-04-30 Open Society Justice Initiative: Justice initiative settles ICC Executive Order lawsuit with the Biden Administration. https://www.justiceinitiative.org/newsroom/justice-initiative-org/newsroom/justice-initiative-settles-icc-executive-order-lawsuit-with-the-biden-administration Download: https://www.justiceinitiative.org/uploads/df5ad29b-deec-45c5-9bab-bb1031a60bcd/osji-v-trump-et-al-4-30-2021.pdf
- 832) 2021-05 FDA: Fact sheet for health care providers emergency use authorization (EUA) of Bamlanivimab and Etesevimab.

 https://www.fda.gov/media/145802/download#:~:text=The%20U.S.%20Food%20and%20Drug,adults%20and%20pediatric%20patients%2C%20including
- 833) 2021-05 Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, Grossman BJ, Henderson JP, Musser J, Salazar E, Hartman WR, Bouivier NM, Liu STH, Pirofski L, Baker SE, van Helmond N, Wright RS, Fairweather D, Bruno KA, Wang Z,

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Paneth NS, Casadevall A, Joyner M: The effect of convalescent plasma therapy on COVID-19 patient mortality: Systematic review and meta-analysis. Mayo Clin Proc, 2021 May; 96 (5): 1262-1275. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7888247/pdf/main.pdf

> ... Importantly, many of the patients enrolled in the studies included in the analyses received convalescent plasma transfusions later in their disease course. In this context, before antibiotics and effective vaccinations, convalescent plasma therapy was widely understood to be most efficacious very early in the course of hospitalizations. 2, 155 As a result, our analysis may underestimate the mortality reduction achievable through early administration of high-titer convalescent plasma for COVID-19.

Conclusion

This real-time systematic review and meta-analysis of contemporaneous studies highlights that the mortality rate of transfused patients with COVID-19 was lower than that of nontransfused patients with COVID-19 and suggests that early transfusion of high-titer plasma represents the optimal use scenario to reduce the risk of mortality among patients with COVID-19. These results favor the efficacy of convalescent plasma as a COVID-19 therapeutic agent.

Acknowledgments

The authors express their gratitude to the convalescent plasma donors. Drs Klassen, Senefeld, Casadevall, and Joyner contributed equally to this article.

- 2021-05-03 Exact Sciences Corp: High sensitivity in a noninvasive colorectal cancer (CRC) screening option¹. In a prospective, head-to-head, point-in-time, 90-site, pivotal study of 10,000 patients aged 50 to 84 years at average risk for CRC, published in The New England Journal of Medicine, Cologuard demonstrated 1*: https://www.cologuardhcp.com/about/clinical-offer
- 2021-05-04 Reuters Fact Check: Fact Check-Red Cross is accepting plasma from people 835) vaccinated against COVID-19. https://www.reuters.com/article/factcheck-redcrossvaccinated/fact-check-red-cross-is-accepting-plasma-from-people-vaccinated-against-covid-19-idUSL1N2MR1HU
- 836) 2021-05-06 Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, et al: The Covid-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. The Lancet, Respiratory Medicine 2021 Jun; 9(6): 622-642. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8102044/pdf/main.pdf
- 2021-05-07 Regeneron Pharmaceuticals: Safety, Tolerability, and Efficacy of Anti-spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients with COVID-19. https://clinicaltrials.gov/ct2/show/NCT04426695?term=REGN-COV2&cond=Covid19&draw=2&rank=3

Regeneron Pharmaceuticals has seven studies posted on NIH https://clinicaltrials.gov and only one listed as a phase I trial (really, this is representative of the NIH designation of Phase I/II seamless trial to de facto avoid PL-115-176). This is legal obfuscation and complete avoidance of the intent of PL-115-176, the Right to Try Act of 2017 (signed by President Trump in 2018), which stipulates that the only requirement that must be met so that a patient can request an

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Investigational Drug or Biologic outside of a clinical trial is that a Phase I clinical trial be "completed." The nominal completion date of NCT04426695 on NIH https://clinicaltrials.gov is May 7, 2021. Conducting "seamless" Phase 1/2 or 1/2/3 Clinical Trials or Phase 2 or Phase 3 Clinical Trials without completion of a Phase 1 Clinical Trial (safety study) are ethically wrong; a violation of the stated intent of the FDA https://www.fda.gov/media/72057/download and NIH https://grants.nih.gov/grants/guide/notice-files/not-od-16-149.html standards which are contrary to these agencies' compliance with statutory mandates of the American people; and I allege that the FDA and the NIH have condoned and facilitated disregard and have violated explicitly that which is stated in PL-155-176, The Right to Try Law - WITH REGARDS TO ALL INVOLVED PARTIES: THIS IS WRONG!

838) 2021-05-09 Monoclonal antibodies' cocktail drug can be game changer in Covid treatment: Experts. The Times of India, May 9, 2021 https://timesofindia.indiatimes.com/city/nagpur/monoclonal-antibodies-cocktail-drug-can-begame-changer-in-covid-treatment-experts/articleshowprint/82487621.cms

> Nagpur: Experts here are expecting the antibody cocktail drug for Covid-19 developed by pharmaceutical giants Roche and Regeneron to work effectively in home-isolated mild to moderate patients who are at high risk of developing severe illness. The therapy was granted emergency use authorization in India a couple of days ago.

Named 'REGN-COV2', the drug is a cocktail of two monoclonal antibodies, Casirivimab and Imdevimab. It is projected to reduce hospitalization by 70%. The drug was tried by former US president Trump after he developed Covid-19 last year.

The therapy is also being looked at something that would help those whose vaccine barrier the virus has breached. It is also expected to be effective on children above 12 years (having body weight more than 40 kg) during the projected third wave when the younger population is likely to be at greater risk of contracting the infection.

Reaserchers is the western world are strongly pushing for yet another combination of monoclonal antibodies, Eli Lilly's Bamlanivimab and Etesivimab, which have a strong data outcome on Covid patients. In March, it received US FDA approval as a potential therapy against variants of SARS-COV2.

A triple combination drug — repurposed Interferon Beta-1b with Lopinavir-Ritonavir and Ribavirin — is also projected to help in reducing the viral load and symptoms. The study has found a place in the 'The Lancet'.

According to senior physician Dr Rajesh Atal, Roche-Renegeron's REGN-COV2 needs to be given at 'entry level' or at an early stage to ensure the spike protein of the SARS-COV2 virus doesn't attaches itself to the cells of the host body. "The drug is to be given on priority to high risk patients like obese people, elderly with comorbidities, diabetic, those ailing having renal issues and so on," he said.

"The drug is expected to work effectively on patients with pre-exposure or early exposure to the disease," said Dr Atal and added, "If one monoclonal antibody fails to act on the mutant virus, the other is expected to shoot it down or reduce the risk."

Infection disease specialist Dr Nitin Shinde, said the cocktail therapy is a good solution for families where one or more members are already infected and others too are showing symptoms. "It's a well formulated 'rescue therapy' which must be administered during the incubation period before the virus gets the better of one," said Dr Shinde.

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He further said that it should be used prophylactically and prove good for those whose vaccine shield is breached. He hoped the cocktail drug would be effective on children above 12 years of age.

Roche Pharma India's managing director V Simpson Emmanuel has said the outpatient treatment of Covid patients with the therapy would 'complement' the vaccination drive in the country.

Well-known senior physician Dr Nikhil Balankhe said studies have shown that the cocktail drug, if introduced at an early stage, is an excellent combination drug to check severe manifestation of the disease.

Dr Satish Deopujari, a well-known paediatrician, feels the monoclonal antibodies would prove to be the game changer in treatment of Covid-9 in the coming days. "The hybrid antibody (combination of Bamlanivimab-Etesevimab and Casirivimab-Imdevimab) has 85% efficacy as compared to other anti-viral drugs in demand now," he said.

Dr Deopujari warned that with major pharmaceutical players set to import the drug, there could be similar chaos as seen in the case of Remdesivir, Tocilizumab, Itolizumab and Bevacizumab. He said the government and ICMR needs to start planning now to ensure only the needy patients gets the therapy.

"This drug will have high demand in the time to come. Blackmarketing and all kinds of malpractices can't be ruled out. The government needs to start working on a strategy immediately. What happened with Remdesivir shouldn't become the case with monoclonal antibody therapy too," he said.

He said the US is following a scoring pattern. "If you fit the criteria only then you would be given the injection. Similarly, we will have to define a high-risk group. There seems to be no planning yet on how it will be rolled out," said Dr Deopujari.

What is monoclonal antibody therapy

A mouse is given antigen injection having tumor cells

The tumor cells get mixed with the plasma cells already in the body to form hybridoma, a hybrid cell

The hybridoma has only one task, that is to produce antibodies

These antibodies produced in huge quantity are called monoclonal

This antibody immediately kills the novel coronavirus

How it became popular

Former US president Donald Trump was one of the early patients on whom this experimental therapy was used

When it must be given

Ideally, in the first three days or maximum up to first 10 days from onset of Covid symptoms

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Major it is administered during OPD treatment in early stage

No other drug has so far same efficacy, provided it is given in the first 3 or 10 days

Limitations

Recommended only for the high risk group like elderly patients and those with comorbidites Cost could be Rs1 lakh or 2lakh per dose as doctors/govt will have to triage patients

In India, indiscriminate use can't be ruled out

Benefits

Prevents hospitalization of mild to moderate patients

Three months passive protection to patient

Could be given before travel or attending an event with big gathering

The cost may go down depending on the agreement with the company

At 85%, it has highest efficacy rate as on date and prevents mortality

- 2021-05-10 McLean T: One year after racist statues toppled in Golden Gate Park, new sculptures could be erected. SFGATE https://www.sfgate.com/bayarea/article/artinstallation-replacing-racist-statues-ggp-sf-16165841.php
- 840) 2021-05-12 Maruhashi T, Higashi Y: Pathophysiological association of endothelial dysfunctions with fatal outcome in COVID-19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8150852/pdf/ijms-22-05131.pdf
- 2021-05-14 Recovery Collaborative Group: Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomized controlled, open-label, platform trial. The Lancet 2021 May 29; 397, Issue 10289: 2049-2059. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00897-7/fulltext Please Note the NIH Clinic Trial NCT04381936 (https://clinicaltrials.gov/ct2/show/NCT04381936) had as its Inclusion Criteria: (i) Hospitalised, (ii) SARS-CoV-2 infection (clinically suspected or laboratory confirmed), and iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial.
- 2021-05-15 U.S. Department of Health and Human Services: COMBATCOVID: Monoclonal antibodies for high-risk COVID-19 positive patients. (above title of COMBATCOVID is: "An official website of the United States government") This is the most recent rendition of this DHHS website as the first "digital photograph of this URL" on the Wayback Machine of the Internet Archive is January 15, 2021. https://web.archive.org/web/20210115190614/https://combatcovid.hhs.gov/i-have-covid-19-

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals Prevention: Active Immunization: Vaccines

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now/monoclonal-antibodies-high-risk-covid-19-positive-patients Below is the initial excerpted paragraphs of that which follows on May 15, 2021. https://web.archive.org/web/20210515023010/https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients:

If you've tested positive for COVID-19, one of the first questions you may have is, *What can I do to reduce the risk of getting sicker?* The good news is, there are treatments that may reduce that risk. Depending on your age, health history, and how long you've had symptoms of COVID-19, you may qualify for a promising form of treatment for the disease. It's called monoclonal antibody (mAb) treatment.

Some early evidence suggests that mAb treatment can reduce the amount of the SARS-CoV-2 virus (the virus that causes COVID-19) in a person's system. This amount is known as viral load. Having a lower viral load means you may have milder symptoms thereby decreasing the likelihood of you being hospitalized.

mAb treatment may help people who:

- Have a positive COVID-19 test, and had symptoms for 10 days or less, and
- Are at high risk of getting more serious symptoms.

Visit the page "How Do I Know If I'm High Risk, and What Do I Do Next?" to learn more.

This page describes what mAbs are, how they can prevent mild to moderate symptoms from getting worse, and what to expect if you get mAb treatment.

- **843)** 2021-05-18 Executive Summary: COVID-19: Pathophysiology of acute disease. The Lancet, Respiratory Medicine. https://www.thelancet.com/series/COVID-19-pathophysiology
- 844) 2021-05-18 Wilt TJ, Kaka AS, MacDonald R, Linskens E, Obley A, Vela K, Duan-Porter W: COVID-19: Remdesivir for Adults A Living Review. Updated February 2021, Health Services Research & Development Service, U.S. Department of Veterans Affairs. https://web.archive.org/web/20210602174519/https://www.hsrd.research.va.gov/publications/esp/covid-19-remdesivir.pdf
- 845) 2021-05-21 Series from the Lancet journals: COVID-19: Pathophysiology of Acute Disease. https://www.lancet.com/series/COVID-19-pathophysiology

Executive Summary

Acute respiratory manifestations are the most common feature of severe COVID-19, but extrapulmonary features of acute disease have also been reported. Emerging evidence indicates that COVID-19 has distinctive pathophysiological features that set the disease apart from respiratory failure of other origins.

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In the first of a Series of four papers, Ignacio Rubio and colleagues provide a comprehensive review of the pathophysiology and phenotypes of COVID-19. The challenges and promise of therapeutically targeting the pleiotropic cytokine interleukin-6 are considered in the second and third papers in the Series. Finally, a fourth paper considers the contributions of viral infection of the alveolar compartment and immunothrombosis of the juxtaposed pulmonary vascular compartment in severe COVID-19. Important questions remain about the clinical complexities and underlying mechanisms of COVID-19. Directions for future research are proposed with the aim of gaining a fuller understanding of the pathophysiology of COVID-19 and subsequently improving management and outcomes for patients.

- **846)** 2021-05-24 BETA DATALAB: The Federal Response to COVID-19: How is the federal government funding relief efforts for COVID-19? https://datalab.usaspending.gov/federal-covid-funding/
- 847) 2021-05-24 Moss C: I'm a vaccinated transplant recipient. I don't have antibodies. Now what? The New York Times, 2021 May 24.

 https://www.nytimes.com/2021/05/24/opinion/organ-transplant-covid-vaccine.html?referringSource=articleShare
- **848)** 2021-05-24 UPMC: Monoclonal antibodies: A treatment option for COVID-19. https://www.upmc.com/coroavirus/monclonal-antibodies
- **849)** 2021-05-24 U.S. Department of Justice. Office of the Solicitor General. https://www.justice.gov/osg/about-office
- 850) 2021-05-25 Colbert S: Interview of Francis Collins, M.D., Ph.D. The Late Show with Stephen Colbert. https://www.youtube.com/watch?app=desktop&v=mi5Uf-Cr73U
- **851)** 2021-05-26 Hinton DM: Emergency Use Authorization 100 regarding Sotrovimab of GlaxoSmithKline LLC. U.S. Food & Drug Administration. https://web.archive.org/web/20210526213011/https://www.fda.gov/media/149532/download
- **852)** 2021-05-26 FDA: Coronavirus (COVID-19) Update: FDA authorizes additional monoclonal antibody for treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-monoclonal-antibody-treatment-covid-19

[This immediate series of references are extremely important and essential to rationalize the errant control over *Passive Immunization* by the FDA and the NIH before the American public over the last 16 months. While it seems the FDA is authorizing another monoclonal antibody in the <u>early</u> treatment arsenal of COVID-19 for the individual, the EUA

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authories Sotrovimab ONLY as an INVESTIGATIONAL BIOLOGIC which is consistent with the EUAs regarding COVID-19 Convalescent Plasma and Regeneron's and Eli Lilly's Monoclonal Antibody Cocktails prohibits the average American from obtaining it. In short, this means (unlike in Japan and India) an individual American who turns COVID-19 positive cannot de facto purchase any of these Passive Immunization agents within 72 hours of diagnosis as they are still INVESTIGATIONAL --not fully, officially authorized biologics by the FDA and the United States government. The FDA and the NIH continue to avoid the intent of (if not violate Federal Law) PL-115-176, the Right to Try Law of 2018.

This is an Ethically Reprehensible methodology being practiced carte blanche by the agencies of U.S. Department of Health and Human Services of which you oversee, Mr. President: To withhold Passive Immunization agents (COVID-19 Convalescent Plasma and Sera and Monoclonal Antibodies and Antibody Cocktails) by rationing by federal misinformation and obfuscation is akin to the Tuskegee Syphilis Project of the midtwentieth century.]

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the investigational monoclonal antibody therapy sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kilograms [about 88 pounds]) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death. This includes, for example, individuals who are 65 years of age and older or individuals who have certain medical conditions.

The safety and effectiveness of this investigational therapy continues to be evaluated for treatment of COVID-19. Sotrovimab is not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. This treatment has not shown benefit in patients hospitalized due to COVID-19 and monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation.

"With the authorization of this monoclonal antibody treatment, we are providing another option to help keep high-risk patients with COVID-19 out of the hospital," said Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research. "It is

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important to expand the arsenal of monoclonal antibody therapies that are expected to retain activity against the circulating variants of COVID-19 in the United States."

Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful antigens such as viruses. Sotrovimab is a monoclonal antibody that is specifically directed against the spike protein of SARS-CoV-2 and is designed to block the virus' attachment and entry into human cells.

2021-05-26 Chen S: FDA authorizes third COVID antibody therapy treatment. AXIOS https://www.axios.com/covid-antibody-therapy-fda-authorization-8417a321-2d3e-4350-aacad909900a01ef.html

> The U.S. Food and Drugs Administration on Wednesday authorized Vir Biotechnology and GlaxoSmithKline's monoclonal antibody drug treatment for early COVID infections, the agency said.

> Why it matters: It's the third antibody treatment authorized for patients in the early stages of the disease who are at high risk of developing severe infections. The drug is "expected" to protect against variants, according to the FDA.

- The two companies in March said an interim study showed the drug was highly effective in reducing hospitalizations or death.
- So far, the U.S. has purchased the treatment directly from manufacturers and offered it to patients through hospitals and health clinics, Wall Street Journal reports.
- Unlike its predecessors, Vir and Glaxo don't have a contract with the federal government, per WSJ. The companies will have to sell the drug commercially.

What they're saying: "With the authorization of this monoclonal antibody treatment, we are providing another option to help keep high-risk patients with COVID-19 out of the hospital," Patrizia Cavazzoni, director of the FDA's Center for Drug Evaluation and Research, said in a statement.

"It is important to expand the arsenal of monoclonal antibody therapies that are expected to retain activity against the circulating variants of COVID-19 in the United States."

- 2021-05-27 Burris S, Anderson ED, Wagenaar AC: The "Legal Epidemiology" of pandemic control. N Engl J Med 2021 May 27; 384 (21): 1973 – 1975. https://www.nejm.org/doi/pdf/10.1056/NEJMp2103380?articleTools=true
- 2021-05-27 Takvorian SU, Guerra CE, Schpero WL: A hidden opportunity Medicaid's role in supporting equitable access to clinical trials. N Engl J Med 2021 May 27; 384 (21): 1975 – 1978. https://www.nejm.org/doi/pdf/10.1056/NEJMp2101627?articleTools=true

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856) 2021-05-28 Cohen K: Opinion: If more children had gotten sick from covid, fewer Americans would have died. The Washington Post, May 28, 2021. https://www.washingtonpost.com/opinions/2021/05/28/what-if-covid-killed-more-children/ (Gamma Globulin was pooled donor serum).

But one story feels very different. In late June 1953, <u>Montgomery County undertook a mass inoculation</u> campaign — not with the Salk vaccine, which was still two years from general use, but with gamma globulin, a substance made from blood plasma that was thought to confer some temporary protection against polio.

The campaign began on a Tuesday. The front page of the Montgomery Advertiser carried a boxed announcement: "White or Black. Have You a Child 9 Years Old or Under? Turn to Page 3-B. The Map Shows You Where to Take Your Child. TODAY THRU FRIDAY. For the GG shot that will save it from Crippling Paralysis." ...

With almost no notice, every single child under 10 was taken to the correct place on the correct day for a treatment that, as the paper explained in a front-page Q&A, didn't always work but "may provide some protection against paralysis."

Question 5: "Is GG a cure for polio?" Answer: "No." And still, 100 percent participation.

So far that year, just 81 Montgomery County residents had contracted polio, and three children had died. And still, 100 percent participation.

Today — with more than 575,000 Americans dead — there are vaccine resisters and anti-maskers and politicians who egg them on. That's already incredible. But if covid victims were mostly children? It would be inconceivable.

- 857) 2021-05-28 Reuters Fact Check: Fact Check-COVID-19 vaccines don't strip people of their antibodies; vaccinated individuals can donate blood.
 https://www.reuters.com/article/factcheck-vaccine-antibodies-plasma/fact-check-covid-19-vaccines-dont-strip-people-of-their-antibodies-vaccinated-individuals-can-donate-blood-idUSL2N2NF0YM
- 858) 2021-05-30 Can antibody cocktail used in Trump's treatment be 'game changer' in India's Covid fight? The Times of India, May 30, 2021, 1-13. https://timesofindia.indiatimes.com/india/how-low-cost-antibody-cocktail-can-be-game-changer-in-indias-covid-fight/articleshow/83089132.cms

NEW DELHI: Last week, an 84-year-old man from Haryana was administered the "famous" anti-Covid cocktail that was also given to former US President Donald Trump.

The monoclonal antibody cocktail has been touted as a "game-changer" in the fight against <u>Covid</u>. Studies have shown that 80% of patients who took the drug did not need hospitalisation.

The most famous example was Trump himself who tested positive last year. Within, he was back at work.

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However, the cost of the drug remains expensive.

Cipla is marketing the drug in hospitals at an estimated price of Rs 59,000 [~\$800 US] per dose. Only one dose is needed.

'A game changer'

In an interview to ANI, Dr Arvinder S Soin of the Medanta Hospital said that production of the monoclonal antibody drug at a reasonable in India could be a "game changer" for the country.

"If these (Monoclonal antibody drug) are made in large enough quantities at a reasonable price. The monoclonal antibodies could be a game changer for India and the world, and especially for high-risk elderly patients and children. There may come a time of the year when anyone testing positive can have monoclonal antibodies, and to avoid serious disease, we should adopt these early," Dr. Soin said.

He pointed out that three specific drugs (monoclonal antibodies drug) authorised by the US Food and Drug Administration (FDA) and one by India's Central Drugs Standard Control Organisation (CDSCO) can 'nip Covid infection in the bud'.

Dr. Soin said that the drug must be given soon after the patient tests positive, and most certainly in the first week of the infection.

This, can prevent severe disease and deaths.

- **859)** 2021-06-01 Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, et al. The COVID-19 puzzle: Deciphering pathophysiology and phenotypes of a new disease entity. The Lancet, The Lancet-Respiratory Medicine SERIES, COVID-19: Pathophysiology of acute disease. June 1, 2021; 9(6), P622-642. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8102044/pdf/main.pdf
- **860)** 2021-06-04 FDA: FDA approves drug to treat smallpox. Disease considered eradicated in 1980 but drug development for smallpox is an important component for medical countermeasure response. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treat-smallpox
- 861) 2021-06-04 Casadevall A, Dragotakes Q, Johnson PW, Senefeld JW, Klassen SA, Wright RS, Joyner MJ, Paneth N, Carter RE: Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality. eLife 2021; 10e69866. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205484/pdf/elife-69866.pdf

Abstract: (Extremely Important!)

...Changes in the number of hospital admissions, SARS-CoV-2 variants, and age of patients could not explain these findings. The retreat from CCP might have resulted in as many as 29,000 excess deaths from mid-November 2020 to February 2021.

Conclusions: A strong inverse correlation between CCP use and mortality per admission in the USA provides population-level evidence consistent with the notion that CCP

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reduces mortality in COVID-19 and suggests that the recent decline in usage could have resulted in excess deaths.

- **862)** 2021-06-07 Terada M, Kutsuina S, Togano T, Saito S, Kinoshita N, Shimanishi Y, Suzuki T, Miyazato Y, Inada M, Nakamoto T, *et. al.*: How we secured a COVID-19 convalescent plasma procurement scheme in Japan. Transfusion 2021 June; 61 (7): 1998-2007. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8242376/pdf/TRF-9999-0.pdf
- **863)** 2021-06-07 U.S. Food and Drug Administration: FDA grants accelerated approval for Alzheimer's drug. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug

Under the accelerated approval provisions, which provide patients suffering from the disease earlier access to the treatment, the FDA is requiring the company, Biogen, to conduct a new randomized, controlled clinical trial to verify the drug's clinical benefit. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.

BUT on 2021-06-10: Joseph A: Third member of FDA expert committee resigns over controversial Alzheimer's therapy decision. STATnews https://www.statnews.com/2021/06/10/third-member-of-fda-expert-committee-resigns-over-controversial-alzheimers-therapy-decision/

- **864)** 2021-06-10 Callahan MV, Poznansky MC: The vaccines we have are good. But they could be so much better. The New York Times, June 10, 2021. https://www.nytimes.com/2021/06/10/opinion/covid-vaccine-strategies.html
- 865) 2021-06-10 California Department of PublicHealth: Monoclonal antibody treatment information for providers and facilities.
 https://web.archive.org/web/20210826051841/https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/Monoclonal-Antibody-Treatment-Information-for-Providers-and-Facilities.aspx
- 866) 2021-06-12 Mohanty KK: COVID-19 treatment: Antibody cocktail used to treat Donald Trump is helping patients in India; here's how—Monoclonal antibodies are targeted towards countering a specific antigen, which is nothing but a foreign element that the immune system recognizes to be a threat. Firstpost https://www.firstpost.com/health/covid-19-treatment-antibody-cocktail-used-to-treat-donald-trump-is-helping-patients-in-india-heres-how-9709411.html
- **867)** 2021-06-15 Steven Colbert: The Late Show with Stephen Colbert on June 15, 2021. https://www.youtube.com/channel/UCMtFAi84ehTSYSE9XoHefig

New York and California announced the end of virtually all pandemic restrictions after both states achieved 70% vaccination, while businesses nationwide continue to drop performative sanitation measures like excessive disinfecting of surfaces

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2021-06-16 Kupferschmidt K: Monoclonal antibodies cut risk of dying from COVID-19—but only in some patients. Science

https://www.sciencemag.org/news/2021/06/monoclonal-antibodies-cut-risk-dying-covid-19only-some-patients

Monoclonal antibodies cut risk of dying from COVID-19—but only in some patients

By Kai KupferschmidtJun. 16, 2021, 1:00 AM

Science's COVID-19 reporting is supported by the Heising-Simons Foundation.

The world's largest trial of COVID-19 therapeutics has for the first time produced convincing evidence that a therapy that directly attacks the virus can save hospitalized patients from death. A combination of antibodies called casirivimab and imdevimab, produced by Regeneron, did not lower mortality when all patients in the study were taken together, investigators of the United Kingdom's Recovery trial announced today—but it reduced deaths by one-fifth among those who did not produce antibodies themselves. A paper with the results will be made available on the medRxiv preprint server later today, the researchers say.

"Here you have really the first direct SARS-CoV-2 drug," says Eric Topol, director of the Scripps Research Translational Institute. Two drugs previously shown to reduce mortality from COVID-19 were developed for other diseases and work by dampening an overactive immune response, which is "kind of an indirect strategy," Topol says.

But Regeneron's antibodies, which attach to the receptor-binding domain of the spike protein and prevent the virus from entering cells, are expensive and not widely available, and quickly identifying patients that benefit from it may be a challenge.

Researchers have developed several monoclonal antibodies against SARS-CoV-2, with mixed results. Some, including Regeneron's, have shown some positive effects on disease progression in outpatients, but none was demonstrated to save the lives of severely ill patients in the hospital. The Recovery trial started to evaluate Regeneron's cocktail in mid-September 2020. By late May, 9785 patients had been randomly allocated to receive either the usual care in the United Kingdom or the usual care plus a one-time infusion of the two antibodies, a procedure that takes roughly 1 hour.

About one-third of the patients were seronegative when they entered the trial, meaning they did not produce antibodies themselves. That includes people with underlying health conditions that weaken their immune system, but also people who, for unclear reasons, are unable to produce antibodies early on. In this group, 30% of patients given standard care died, versus 24% of those who received the antibody cocktail. That translates to six lives saved for every 100 such patients treated with the drug.

The Regeneron cocktail received a lot of attention when former U.S. President Donald Trump received it during his bout with COVID-19 in October 2020. Although it's not clear whether Trump's immune system produced antibodies, the new results suggest the treatment may have helped save his life, Topol says: "Who knows what might have happened at his age, with his morbid obesity and all the other risk factors that he had."

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Although it received an emergency use authorization from the U.S. Food and Drug Administration in November 2020—and the U.S. government bought 1.5 million doses— Regeneron's therapy has not been widely used in the United States, Topol says. "This is just sitting on shelves," he says. "I think [the Recovery trial] is going to wake people up as to the benefit."

But doctors will have to determine which patients fail to produce antibodies. "I think this isn't a complicated test to run, it just needs to be done," says Martin Landray of the University of Oxford, one of Recovery's principal investigators.

A bigger challenge may be cost. "We anticipate, but we don't know this, that they may be around £1000 or £2000 per treatment," Recovery co-investigator Peter Horby said at a press conference on Tuesday. That might put the therapy and many similar ones in the pipeline out of reach for most people living in developing countries, which also have far fewer COVID-19 vaccine doses than rich countries. Access to antibody drugs in general has been particularly unequal across the globe, says Lindsay Keir, a pediatrician who co-authored a Wellcome Trust report on global access to such treatments released last year. "Antibodies that we have benefited from in highincome countries for 20, 30 years, still aren't available in many countries," Keir says.

The inequity is a "scandal," Horby says. "There really must be an initiative to make these drugs accessible, and that requires two things: They have to be available, which means we have to scale up manufacturing, and they have to be affordable, which means we have to reduce the prices."

2021-06-16 Ellyatt H: Regeneron antibody 'cocktail' can save lives in hospitalized Covid patients, study finds. CNBC. https://www.cnbc.com/2021/06/16/regeneron-antibody- cocktail-can-save-lives-in-hospitalized-covid-patients.html

Regeneron antibody 'cocktail' can save lives in hospitalized Covid patients, study finds

PUBLISHED WED, JUN 16 20215:42 AM EDT UPDATED WED, JUN 16 20217:06 AM EDT

KEY POINTS

- Another potentially life-saving treatment for hospitalized Covid-19 patients has been discovered by researchers at the University of Oxford.
- An antibody combination made by Regeneron reduces the risk of death when given to patients with severe Covid who have not mounted a natural antibody response of their own.
- The study was part of the wider Recovery trial investigating various possible treatments for people hospitalized with coronavirus.

LONDON — Another potentially life-saving treatment for hospitalized Covid-19 patients has been discovered by researchers at the University of Oxford.

--- May 30, 2022 -----

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

The British study — part of the wider Recovery trial investigating various possible treatments for people hospitalized with coronavirus — found that an antibody combination made by Regeneron reduces the risk of death when given to patients with severe Covid who have not mounted a natural antibody response of their own.

The treatment uses a "cocktail" of two monoclonal antibodies (casirivimab and imdevimab, known as Regen-Cov in the U.S.) that bind specifically to two different sites on the coronavirus spike protein, neutralizing the ability of the virus to infect cells.

Previous studies in nonhospitalized Covid patients have shown that the treatment reduces viral load, shortens the time to the resolution of symptoms, and significantly reduces the risk of hospitalization or death.

But in a small trial in hospitalized patients, preliminary evidence suggested a clinical benefit for patients who had not mounted a natural antibody response of their own (that is, they were seronegative) when they entered the trial.

This latest study is the first trial large enough to determine definitively whether this treatment reduces mortality in patients hospitalized with severe Covid.

The trial, which took place between September and May, involved 9,785 patients hospitalized with Covid.

For patients who were seronegative at the start of the study, the antibody combination significantly reduced their chances of dying by one-fifth compared with those receiving usual care alone (that is, 24% of patients in the antibody combination group died versus 30% of patients in the usual care group).

Thus, for every 100 such patients treated with the antibody combination, there would be six fewer deaths.

As well as reducing the risk of death, for the seronegative patients who received the antibody combination treatment, the duration of hospital stay was four days shorter than for those receiving usual care. The chances of needing a ventilator was also lower.

The treatment had no noticeable beneficial effect on patients who were seropositive at the start of the trial.

The preliminary results from the trial, which will soon be submitted to a leading peer-reviewed medical journal, could determine how Covid patients are treated in future in hospital, one expert noted.

"It means that patients being hospitalised with Covid-19 can be divided into two groups based on whether or not they have made antibodies to the virus," Fiona Watt, executive chair of the U.K.'s Medical Research Council, said in a statement.

"If they do not have antibodies then treatment with antibody-based drugs to the spike protein can reduce their risk of death and also time spent in hospital. Patients who have made their own antibodies to the virus do not benefit from the new treatment, which is important information given the cost of drugs."

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Peter Horby, professor of emerging infectious diseases in the Nuffield Department of Medicine at the University of Oxford, and the joint chief investigator for the Recovery trial, described the results as "very exciting."

"The hope was that by giving a combination of antibodies targeting the SARS-CoV-2 virus we would be able to reduce the worst manifestations of Covid-19. There was, however, great uncertainty about the value of antiviral therapies in late-stage Covid-19 disease. It is wonderful to learn that even in advanced Covid-19 disease, targeting the virus can reduce mortality in patients who have failed to mount an antibody response of their own," he said in a statement.

The Recovery trial has already made several life-saving discoveries, one being that dexamethasone, a cheap and widely used steroid, was able to save lives among severely ill Covid patients. Last week it published the results of another trial that showed aspirin did not improve the survival rates for patients hospitalized with Covid who are at an increased risk of blood clots.

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- 2021-06-20 Dickerson J: John Dickerson interviews Scott Gottlieb, M.D. on Face the 871) Nation, June 20, 2021. https://www.cbsnews.com/news/transcript-scott-gottlieb-face-thenation-06-20-2021/

DR. GOTTLIEB: That's right, and I think that this could be a real game changer. This is a virus that we should be able to drug. The machinery that this virus uses to replicate are things that we've drugged before. It's not a-it's not a very wily virus. It's not a virus that should evade our drug development tools. So I think that we will have a drug that inhibits viral **replication.** Pfizer, the company I'm on the board of, is working on one. Merck is working on another one in advanced development. There's a number of other companies also engaged in this pursuit. I think we will get a drug that inhibits viral replication that could be taken on an outpatient basis and is basically like a Tamiflu for coronavirus that you could take when you first have symptoms, when you first have a diagnosis to prevent the progression to disease.

- 2021-06-21 Merrilles A: Washington U researchers show COVID-19 treatment often effective against virus variants, in study of rodents. The St. Louis Post-Dispatch https://www.stltoday.com/news/local/metro/washington-u-researchers-show-covid-19treatment-often-effective-against-virus-variants-in-study-of/article 34089b54-7f2e-549a-904d-c4dacbffa031.html
 - i. Several monoclonal antibody treatments are currently available in the U.S. under emergency use authorization from the FDA. They are injected as early as possible during a patient's illness, and are often used for patients in more vulnerable groups, who are at higher risk of eventually having severe cases.

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- 878) 2021-07-08 NIH—COVID-19 Treatment Guidelines, Clinical Management Summary, Last Updated: July 8, 2021, pages 40-42. https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

Clinical Management Summary

Last Updated: July 8, 2021

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

The clinical spectrum of SARS-CoV-2 infection includes asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness. Figure 1 provides guidance for clinicians on the therapeutic management of nonhospitalized adult patients. This includes patients who do not require hospitalization or supplemental oxygen and those who have been discharged from an

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

emergency department or a hospital. Figure 2 provides guidance on the therapeutic management of hospitalized adult patients according to their disease severity and oxygen requirements.

Figure 1. Therapeutic Management of NonHospitalized Adults with COVID-19

All outpatients with COVID-19 who enter the health care system should have in-person or telehealth follow-up visits. Symptomatic treatments, including hydration, antipyretics, analgesics, and antitussives, can be initiated as needed.

Patients should be counseled about symptoms that warrant re-evaluation by a health care provider (e.g., new onset dyspnea, worsening dyspnea [particularly dyspnea that occurs while the patient is resting or that interferes with daily activities], mental status changes). Home resources should be assessed before patients are discharged from a clinic, urgent care center, ED, or hospital; outpatients should have access to housing, proper nutrition, a caregiver, and a device that is suitable for telehealth. If patients are discharged while they are still receiving oxygen supplementation, they should receive oximetry monitoring and close follow-up soon after discharge.

PATIENT DISPOSITION

PANEL'S RECOMMENDATIONS

Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit

Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progres sion, as defined by the EUA criteria (treatments are listed in alphabetical order):"

- · Casirivimab plus imdevimab: or
- Sotrovimab

At this time, the Panel recommends against the use of bamlanivimab plus etesevimab in these patients due to an increase in the proportion of potentially resistant variants (AIII).ª See text for details.

The Panel recommends against the use of dexamethasone or other systemic glucocorticoids in the absence of another indication (AIII).19

Discharged From Hospital Inpatient Setting in Stable Condition and Does

The Panel recommends against continuing the use of remdesivir (Alla), dexamethasone (Alla), or baricitinib (Alla) after hospital discharge.

Discharged From Hospital Inpatient Setting and Requires Supplemental

There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.

Discharged From ED Despite New or Increasing Need for Supplemental

close follow-up is ensured

The Panel recommends using dexamethasone 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events (BIII).

There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for

The Panel recommends against the use of baricitinib in this setting, except in a clinical trial (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

- In laboratory studies, some SARS-CoV-2 variants of concern or interest harbor certain mutations that are associated with reduced susceptibility to certain agents Some regimens may be preferred in certain settings based on the degree of reduced susceptibility and the prevalence of these variants in a given region. See Anti-SARS-CoV-2 Monoclonal Antibodies and the Panel's statement on the EUAs for anti-SARS-CoV-2 monoclonal antibodies for more information. Updates on the distribution of bamlanivimab plus etesevimab are available on the HHS Bamlanivimab/Etesevimab website
- * There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause
- These individuals should receive eximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic visits.
- In cases where resources (e.g., inpatient beds, staff members) are scarce, it may be necessary to discharge an adult patient and provide an advanced level of home. care, including supplemental oxygen (whether patients are receiving oxygen at home for the first time or are increasing their baseline oxygen requirements), pulse oximetry, and close follow-up through visiting nurse services, telehealth, or in-person clinic visits.

Key: ED = emergency department; EUA = Emergency Use Authorization; HHS = Department of Health and Human Services; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

COVID-19 Treatment Guidelines

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Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

DISEASE SEVERITY

PANEL'S RECOMMENDATIONS

Hospitalized but Does Not Require Supplemental Oxygen The Panel recommends against the use of dexamethasone (Alla) or other corticosteroids (AllI).

There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.

Hospitalized and Requires Supplemental Oxygen Use one of the following options:

- Remdesivir^{b.c} (e.g., for patients who require minimal supplemental oxygen) (Blla)
- Dexamethasone^d plus remdesivir^{b,c} (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII)
- Dexamethasone^d (when combination therapy with remdesivir cannot be used or is not available) (BI)

Hospitalized and Requires
Oxygen Delivery Through a
High-Flow Device or Noninvasive
Ventilation

Use one of the following options:

- Dexamethasoned (AI)
- Dexamethasone^d plus remdesivir^{b,c} (BIII)

For patients who were recently hospitalized* with rapidly increasing oxygen needs and systemic inflammation:

 Add either baricitinib^{to} (Blla) or tocilizumabth (Blla) to one of the two options above

Hospitalized and Requires IMV or ECMO

For most patients:

• Dexamethasoned (AI)

For patients who are within 24 hours of admission to the ICU:

• Dexamethasonedi plus tocilizumab(h (Blla)

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

- Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.
- The dose for remdesivir is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
- For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, IMV, or ECMO, remdesivir should be continued until the treatment course is completed.
- The dose for dexamethasone is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
- * For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.
- As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
- The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge (refer to Table 4c for dose modifications for patients with renal impairment). Baricitinib should be used in combination with steroids (with or without remdesivir). The combination of baricitinib plus tocilizumab has not been studied, and the Panel recommends against the use of this combination, except in a clinical trial (AllI).
- * The dose for toolitzumab is 8 mg/kg of actual body weight (up to 800 mg) administered as a single fV dose. The combination of toolitzumab plus bariotinib has not been studied, and the use of this combination should be avoided outside of a clinical trial. See the Interleukin-6 Inhibitors section for more information.
- ¹ The combination of dexamethasone plus remdesivir may be considered for patients who have recently been intubated (CIII). The Panel recommends against the use of remdesivir monotherapy in these patients.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMV = invasive mechanical ventilation; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

COVID-19 Treatment Guidelines

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 Transcript: https://www.cbsnews.com/news/transcript-dr-anthony-fauci-on-face-the-nation-july-11-2021/

DR. FAUCI: Well, I think maybe all of the above, you know, it is almost inexplicable why people, when they see the data in front of them that they don't get vaccinated. We have a Delta variant that you mentioned, John, that is easily transmissible much more easily and readily and efficiently from person to person than the other viruses, the other variants that we've dealt with. That's the first thing. The second thing, the data that's hitting you right between the eyes is that ninety nine point five percent of all the deaths to COVID-19 are in unvaccinated people.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals **Prevention:** Active Immunization: Vaccines

states with low vaccination rates more than <u>99 percent</u> of covid-19 deaths over the past six months were among unvaccinated people.

- 886) 2021-07-20 Nikkei staff writers: Japan approves COVID antibody cocktail used to treat Trump Roche unit's offering holds promise as a tool against worsening cases. NIKKEI Asia, July 20, 2021 https://asia.nikkei.com/Spotlight/Coronavirus/Japan-approves-COVID-antibody-cocktail-used-to-treat-Trump
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ABSTRACT RESULTS

Among 1497 fully vaccinated health care workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The B.1.1.7 (alpha) variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (Ct value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented.

CONCLUSIONS

Among fully vaccinated health care workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period. Most breakthrough infections were mild or asymptomatic, although persistent symptoms did occur.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals **Prevention**: Active Immunization: Vaccines

2021-07-30 Hinton DM: EUA 091 authorizing *Post-Exposure Prophylaxis*. 892) https://www.regeneron.com/downloads/treatment-covid19-eua-fda-letter.pdf https://www.fda.gov/media/145610/download

> REGEN-COV may only be used in adult and pediatric individuals (12 years of age and older weighting at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or deaths, and are:

Not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications

have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease control and Prevention or who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARSp-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

...only be used in adult and pediatric individuals (12 years of age and older weighting at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or deaths, and are

- 2021-08 Mayo Clinic: Different types of COVID-19 vaccines: How they work. https://web.archive.org/web/20210806124201/https://www.mayoclinic.org/diseasesconditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465
- 894) 2021-08-02 Shammas B, Suliman A, Pietsch B: U.S. hits Biden's vaccination goal a month late, with 70% of adults receiving at least one shot. The Washington Post, August 2, 2021. https://www.seattletimes.com/nation-world/u-s-hits-bidens-vaccination-goal-a-monthlate-with-70-of-adults-receiving-at-least-one-shot/
- 2021-08-02 Reality Check team, BBC News: Coronavirus: Was US money used to fund risky research in China? BBC News. https://www.bbc.com/news/57932699
- **896**) 2021-08-05 NIH—COVID-19 Treatment Guidelines, Clinical Management Summary, Last Updated: August 5, 2021, pages 40-42. https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

Clinical Management Summary

Last Updated: July 8, 2021

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

----- May 30, 2022 -----

The clinical spectrum of SARS-CoV-2 infection includes asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness. Figure 1 provides guidance for clinicians on the therapeutic management of nonhospitalized adult patients. This includes patients who do not require hospitalization or supplemental oxygen and those who have been discharged from an emergency department or a hospital. Figure 2 provides guidance on the therapeutic management of hospitalized adult patients according to their disease severity and oxygen requirements.

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- **899)** 2021-08-10 FDA authorizes REGEN-COV monoclonal antibody therapy for post-exposure prophylaxis (prevention) for COVID-19. *Prophylaxis with REGEN-COV is not a substitute for vaccination against COVID-19*. https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-regen-cov-monoclonal-antibody-therapy-post-exposure-prophylaxis-prevention-covid-19
- **900)** 2021-08-10 Mayo Clinic Staff: COVID-19 vaccines for kids: What you need to know. https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/covid-19-vaccines-for-kids/art-20513332
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- **907)** 2021-08-17 Benen S: As COVID slams Fla., DeSantis focuses on treatment, not prevention. https://www.msnbc.com/rachel-maddow-show/covid-slams-fla-desantis-focuses-treatment-not-prevention-n1276981
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 20kids:sem.ga:p:RG:GM:gen:PTN.Grants:FY21
- **909)** 2021-08-18 Whitely J: Why is Gov. Abbott receiving Regeneron treatment if he has no COVID-19 symptoms? Gov. Abbott remained quiet on his first full day in quarantine in the governor's mansion. Abbott's office did not provide an update on his condition. Texas News https://www.wfaa.com/article/news/local/texas/why-gov-abbott-receiving-regeneron-treatment-no-covid-19-symptoms/287-22b6ea37-9784-42a2-8e54-03235f451882
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 https://web.archive.org/web/20210820092946/https://www.fda.gov/media/145611/download
 On page 25 of 56:

Obesity or being overweight (for example, BMI >25 kg/m²

A BMI>25 kg/m² which is greater than two-thirds of the Adult population of America!

Monaco K: Over 73% of U.S. adults overweight or obese—Obesity rate up by half since 1999-2000, NHANES data indicate; nearly 10% severely obese. MedPage Today, December 11, 2020. https://www.medpagetoday.com/primarycare/obesity/90142 or https://www.medpagetoday.com/primarycare/obesity/90142 or https://www.medpagetoday.com/primarycare/obesity/90142 <a href="https://www.medpagetoday.com/primarycare/

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More than 93.8 percent of the U.S. is at substantial or high level of risk for community transmission of SARS-CoV-2, according to the Centers for Disease Control and Prevention (CDC). CDC defines an area to be at high risk when either the number of new cases in a county exceeds 100 per 100,000 persons, or more than 10 percent of COVID-19 tests come back positive in the past seven days. In those areas, CDC recommends wearing a mask indoors in public to maximize protection from the Delta variant and prevent spreading it to others.

- 919) 2021-08-20 UPMC: Monoclonal Antibodies: A treatment option for CVOID-19. Printed out 8/20/2021. https://www.upmc.com/coronavirus/monoclonal-antibodies
- 920) 2021-08-23 Malarkey MA, Gruber MF: Biologics License Application approval for Comirnaty, Pfizer-BioNTech COVID-19 mRNA Vaccine: BL 125742/0. https://www.fda.gov/media/151710/download
- 921) 2021-08-23 Hinton DM: Reissues the EUA for the Pfizer COVID-19 Vaccine to clarify the issue of the BLA 125742/0 approval. https://www.fda.gov/media/150386/download

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals **Prevention:** Active Immunization: Vaccines

On August 23, 2021, FDA approved the biologics license application (BLA) submitted by BIONTech Manufacturing GmbH for COMIRNATY (COVID-19 Vaccine, mRNA) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

On August 23, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 12, 2021 letter of authorization in its entirety with revisions incorporated to clarify that the EUA will remain in place for the Pfizer-BioNTech COVID-19 vaccine for the previously-authorized indication and uses, and to authorize use of COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved BLA. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to provide update language regarding warnings and precautions related to myocarditis and pericarditis. The Fact Sheet for Recipients and Caregivers was updated as the Vaccine Information Fact Sheet for COVID-19 Vaccine and information about the FDA-licensed vaccine, COMIRNATY (COVID-19 Vaccine, mRNA).

Pfizer-BioNTech COVID-19 Vaccine contains a nucleoside-modified messenger RNA (modRA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 formulated in lipid particles. COMIRNATY (COVID-19 Vaccine, mRNA) is the same formulation as the Pfizer-BioNTech COVID-19 Vaccine and can be used interchangeably with the Pfizer-BioNTech COVID-19 Vaccine to provide the COVID-19 vaccination series.⁸

2021-08-23 FDA: FDA approves first COVID-19 Vaccine. (Marketed as Comirnaty) https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine FDA: Comirnaty and Pfizer-BioNTech COVID-19 Vaccine https://www.fda.gov/emergencypreparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizerbiontech-covid-19-vaccine

> Example NBC report regarding this approval with Dr. Fauci response. https://www.nbc.com/today/video/today-in-30-august-24-dr-anthony-fauci-coronavirus-and-theclassroom/345221659

- 2021-08-24 Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta KD, House T, Hay J, Bell JI, Newton JN, Farrar J, Crook D, Cook D, Rourke E, Studley R, Peto T, Diamond I, Walker S, the COVID-19 Infection Survey Team. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. medRxiv https://www.medrxiv.org/content/10.1101/2021.08.18.21262237v1
- 2021-08-24 Zients J, Walensky R, Fauci A, Murthy V: Press briefing by White House COVID-19 response team and public health officials. Transcript: https://www.whitehouse.gov/briefing-room/press-briefings/2021/08/24/press-briefing-bywhite-house-covid-19-response-team-and-public-health-officials-51/

DR. FAUCI: Thank you very much, Dr. Walensky. I'd like to spend the next couple of minutes in addressing a much-underutilized intervention for COVID-19, and that is the use of monoclonal antibodies for the TREATMENT and PREVENTION of SARS-CoV-2 infection and COVID-19 disease.

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Next slide.

For those not totally familiar with this, monoclonal antibody is an antibody that's produced by a single clone of B cells or a cell line, and consists of identical antibody molecules that can actually be produced in the in-vitro situation in unlimited quantities.

Next slide.

If you look at the virion on the upper-left part of the slide and you look up the blown-up spike protein — the red molecule on the right upper panel — when you talk about polyclonal antibodies, which result from infection or vaccination, it's a group of antibodies against every aspect of the spike protein, which is the good news. However, the concentration and the affinity of those antibodies can be markedly improved if you get a single cloned antibody — hence the word "monoclonal" — that's against the very specific part of the spike protein that can have a major effect in prevention and treatment.

Next slide.

So, let's look at what we have. We have three anti-SARS-CoV-2 monoclonal antibody products that have currently had Emergency Use Authorization from the FDA. And the EUAs here are for adults and children 12 years of age and older who weigh at least 88 pounds.

There are three of them. There's the Lilly product — the bamlanivimab plus etesevimab. There's the Regeneron project — product, referred to as REGEN-COV. And then there's the GSK and Vir product. Each of these products targets the spike protein of SARS-CoV-2.

Next slide.

So, you can do an indication for these antibodies that are twofold. The first is to treat infection with SARS-CoV-2.

Next slide.

And in this regard, clinical trials have demonstrated that early treatment with anti-SARS-CoV-2 monoclonal antibodies can reduce the risk of COVID-19 hospitalization or death by 70 to 85 percent.

It is important to emphasize that this must be done early in infection and not wait, of course, until a person is sick enough to be hospitalized. That's when you get the best effect.

And again, being an underutilized intervention, we want people out there, including physicians, as well as potential patients, to realize the advantage of this very effective way of treating early infection.

Next slide.

Now, if you look at the people who should benefit from this, this is a list from the FDA and the NIH treatment guidelines about all of the people who may have significant benefit from this type of therapy if given early in their infection.

I'm not going to go through each and every one of them, but as you can see, there are a number of

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

conditions on this slide that could benefit from the monoclonal antibody treatment after infection.

Next slide.

But there's also the benefit of prevention using monoclonal antibodies.

Next slide.

And we know now that the FDA, just a couple of weeks ago, authorized the Regeneron monoclonal antibody for post-exposure prophylaxis, namely for the prevention of COVID-19 after someone has been exposed to a documented case of SARS-CoV-2.

And even now — and I won't show the data because of lack of time — there are now studies in pre-exposure prophylaxis, as well as other studies in treatment.

So, I'll have on the last slide — next slide — the treatment guidelines panel. We can give you all the information, and it's accessible on the website shown here. And for physicians, patients, and others who want to know how you can get monoclonal antibodies administered, this is the call center and this is the online way to approach it.

So, bottom line is: This is a very effective intervention for COVID-19. It is underutilized, and we recommend strongly that we utilize this to its fullest.

YouTube (Fauci slide show: 10:22 – 15:27 minutes in presentation) https://www.youtube.com/watch?v=AZNP05w2cxU

- 925) 2021-08-25 NIH/NLM: MedlinePlus—Trusted Health Information for You. Gene Therapy and Other Advances. Chapter 6: What are mRNA vaccines and how do they work? https://web.archive.org/web/20210825084027mp_/https://medlineplus.gov/download/genetics/understanding/therapy.pdf
- 926) 2021-08-26. Salter J: New Missouri sites announced for monoclonal antibody infusion treatments. https://www.ksdk.com/article/news/health/coronavirus/new-missouri-sites-monoclonal-antibody-infusion-treatments/63-2905c735-0e9e-41f0-99df-75ed44cd063e
- 927) 2021-08-26 Senator Ron Johnson: Letter to FDA Acting Commission Janet Woodcock, M.D. U.S. Senate. https://www.hsgac.senate.gov/imo/media/doc/2016-09-19%20RHJ%20to%20FDA%20Califf%20declined%20invite.pdf

In the letter that reissued the EUA for the Pfizer-BioNTech COVID-19 vaccine, the FDA stated that Comirnaty and the Pfizer-BioNTech COVID-19 vaccines are "legally distinct with certain differences that do not impact safety or effectiveness." That statement, together with the fact that the FDA issued two distinct letters – one extending the EUA for the vaccine used in the U.S. and the other granting the FDA approval of the Comirnaty vaccine used in Europe and other countries – has caused a great deal of confusion.

- 928) 2021-08-27 Hinton DM: ID NOW COVID-19 EUA200074 for Abbott Diagnostics qualitative detection of nucleic acid of SARS-CoV-2 virus. https://www.fda.gov/media/136522/download
- 929) 2021-08-27 Centers for Medicare & Medicaid Services (CMS.gov): Monoclonal antibody COVID-19 infusion. https://www.cms.gov/medicare/covid-19/monoclonal-antibody-covid-19-infusion
- 930) 2021-08-27 CDC, COVID-19: CDC recommends use of Johnson & Johnson's Janssen COVID-19 vaccine resume. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/JJUpdate.html
- 931) 2021-08-30 KMOV.COM Staff: Monoclonal antibody treatment center coming to St. Louis City. https://www.kmov.com/news/monoclonal-antibody-treatment-center-coming-to-st-louis-city/article-e1f92a34-090b-11ec-aba6-db344cba84e7.html
- 932) 2021-08-30 Hick JL, Hanfling D, Wynia MK, Toner E: Crisis standards of care and COVID-19: What did we learn? How do we ensure equity? What should we do? Nam.edu/Perspectives. https://nam.edu/crisis-standards-of-care-and-covid-19-what-did-we-learn-how-do-we-ensure-equity-what-should-we-do/
- 933) 2021-08-30 Wilt TJ, Kaka AS, MacDonald R, Linskens E, Obley A, Vela K, Duan-Porter W: COVID-19: Remdesivir for Adults A Living Review. U.S. Department of Veterans Affairs, Veterans Health Administration, Health Services Research & Development Service (HSR&D), Evidence Synthesis Program.
 https://www.hsrd.research.va.gov/publications/esp/covid-19-remdesivir.pdf Unable to be accessed on 1/23/2022. But with the Wayback Machine, one can access a 35 page document of May 18, 2021 and a 33 page document of February 17, 2021 published by VHA Health Services Research & Development Service (HSR&D). Wilt TJ, Kaka AS, McDonald R, Linskens E, Obley A, Vela K, Duan-Porter W: COVID-19: Remdesivir for Adults A living Review, Updated May 2021. VHA Health Services Research & Development Service (HSR&D).

https://web.archive.org/web/20210602174519/https://www.hsrd.research.va.gov/publications/esp/covid-19-remdesivir.pdf

WHAT'S NEW

Updated May 18, 2021

Search current as of May 10, 2021

Next update expected August 31, 2021 This update revises findings from our second update of February 2021 and includes a literature search through May 10, 2021. One new small, single-center, high risk of bias RCT compared a 5-day course of remdesivir to standard of care (SC) in adults hospitalized with severe COVID-19. In per-protocol analysis, remdesivir as compared to SC did not reduce mortality, need for invasive mechanical ventilation, or frequency of adverse events. Results align with previous conclusions that remdesivir probably results in little to no difference in mortality or subsequent need for ventilation. Given the study's high risk of bias, we did not include it in aggregate certainty of evidence. ratings. Our

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

original conclusions regarding certainty and strength of evidence on effectiveness of remdesivir for adults with COVID-19 remain unchanged.

WHAT DID WE KNOW? Our prior VA-ESP report of 5 randomized trials (RCTs) concluded that in hospitalized adults with COVID-19, remdesivir probably results in little to no reduction in mortality, a moderate increase in percent recovered, and a moderate reduction in serious adverse events.1 Effects on mortality may vary by initial respiratory support but not by other patient or disease factors. Effect on hospital length of stay or percent hospitalized is mixed (3 RCTs), in part due to continued hospitalization while administering remdesivir. For adults not receiving mechanical ventilation or extracorporeal membrane oxygenation, a 5-day course of remdesivir may provide benefits over, and fewer harms than, a 10-day course. Trials excluded pregnant women or those with severe hepatic or renal dysfunction. On October 22, 2020 the FDA approved remdesivir for patients over age 12 and weighing more than 40kg hospitalized with COVID-19.2 The FDA has noted side effects of remdesivir.3 Remdesivir is the only drug so far to receive federal approval for COVID-19. WHAT IS NEW? Updated: 05/18/2021 Search current as of 5/10/2021 This update adds 1 RCT (high risk of bias), giving a total of 6 included RCTs,4-9 and revises findings from our second update of February 2021.1 The new RCT was a small single-center study from India that compared a 5-day course of remdesivir to standard of care (SC) in adults hospitalized with severe COVID-19.9 In per-protocol analysis, remdesivir as compared to SC did not reduce mortality, need for invasive mechanical ventilation, or frequency of adverse events. Results align with previous conclusions that remdesivir probably results in little to no difference in mortality or subsequent need for ventilation. Given the study's high risk of bias, we did not include it in aggregate certainty of evidence. Summary of conclusions and updated findings are detailed in Table 1. WHAT DO WE CONCLUDE? The results of this new study did not change our prior conclusion that overall, a 10-day remdesivir course probably results in little to no reduction in mortality (4 RCTs). Remdesivir may result in a small reduction in proportion on mechanical ventilation (3 RCTs) but probably results in little to no difference in new need for ventilation versus SC (1 RCT). Remdesivir probably results in a moderate increase in percent recovered, a moderate decrease in serious adverse events, and may result in a large reduction in time to recovery. Effect on hospital length of stay or percent remaining hospitalized is mixed. Effects on mortality may vary by initial respiratory support but not by other patient or disease factors including symptom or COVID-19: Remdesivir for Adults (updated May 2021) Evidence Synthesis Program 2 hospitalization duration, age, sex, race/ethnicity, smoking status, comorbidities, geographic location, or corticosteroid use. Remdesivir may increase mortality in those already on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Recovery effects may not vary by age, sex, symptom duration, or disease severity. Remdesivir probably reduces serious adverse effects that include measures of COVID-19 disease progression. Compared with 10 days, a 5-day remdesivir course may reduce mortality and need for mechanical ventilation, may increase recovery and/or clinical improvement by small to moderate amounts, and may reduce serious adverse events among patients not requiring mechanical ventilation at baseline. Drug costs would be lower. Pregnant women, children under age 12, and individuals with severe renal and hepatic dysfunction have been excluded from studies. Caution and monitoring are indicated if remdesivir is used in these individuals. The FDA notes that remdesivir side effects include elevated liver enzymes and allergic reactions (which may include changes in blood pressure and heart rate, low blood oxygen level, fever, shortness of breath, wheezing, swelling (eg, lips, around eyes, under the skin), rash, nausea, sweating, or shivering)

WHAT'S NEW

Updated February 17, 2021

Search current as of February 8, 2021

Next update expected April 2021 This update revises findings from our first update of November 2020 and includes a literature search through February 8, 2021. No new trials were identified. However, the largest RCT on remdesivir – Solidarity – is newly available as a peer-reviewed publication (previously available as

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

a non-peer review preprint). Our updated findings include new analyses and data on recovery/improvement, need for ventilation, hospital length of stay, and percentage of patients hospitalized between days 7-14. We also provide new mortality analyses by subgroups.

WHAT DID WE KNOW? Our prior VA-ESP report of 5 randomized trials (RCTs) concluded that in hospitalized adults with COVID-19, remdesivir probably results in little to no reduction in mortality, a moderate increase in percent recovered, and a moderate reduction in serious adverse events. Effect on hospital length of stay or percent hospitalized is mixed (3 RCTs) in part due to continued hospitalization while administering remdesivir. For adults not receiving mechanical ventilation or extracorporeal membrane oxygenation, a 5-day course of remdesivir may provide similar benefits to, and fewer harms than, a 10-day course. Trials excluded pregnant women or those with severe hepatic or renal dysfunction. On October 22, 2020 the FDA approved remdesivir for patients over age 12 and weighing more than 40kg hospitalized with COVID-19.² Remdesivir is the only drug so far to receive federal approval for COVID-19. WHAT IS NEW? Updated: 02/17/2021 Search current as of 2/8/2021 This update revises findings from our first update of November 2020 and also includes a literature search through February 8, 2021. This update includes 5 RCTs, ⁴⁻⁸ similar to the prior report. However, the largest RCT on remdesivir – Solidarity is newly available as a peerreviewed publication (previously available as a non-peer review pre-print). Our updated findings include new analyses and data on recovery/improvement, need for ventilation, hospital length of stay, and percentage of patients hospitalized between days 7-14. We also provide new mortality analyses by subgroups defined by baseline respiratory support requirements: no oxygen, requiring supplemental oxygen but not ventilation, and requiring ventilation. Summary of conclusions and updated findings are detailed in Table 1. WHAT DO WE CONCLUDE? Overall, a 10-day remdesivir course probably results in little to no reduction in mortality (4 RCTs). Remdesivir may result in a small reduction in proportion on mechanical ventilation (3 RCTs) but probably results in little to no difference in new need for ventilation versus standard care (1 RCT). Remdesivir probably results in a moderate increase in percent recovered, a moderate decrease in serious adverse events, and may result in a large reduction in time to recovery. Effect on hospital length of stay or percent remaining hospitalized is mixed. Effects on mortality may vary by initial respiratory support but not by other patient or disease factors including: symptom or hospitalization duration, age, sex, race/ethnicity, smoking status, comorbidities, geographic location, or corticosteroid use. Remdesivir may increase mortality in those already on invasive mechanical ventilation or extracorporeal membrane oxygenation COVID-19: Remdesivir for Adults (updated Feb 2021) Evidence Synthesis Program 2 (ECMO). Recovery effects may not vary by age, sex, symptom duration, or disease severity. Remdesivir probably reduces serious adverse effects that include measures of COVID-19 disease progression. Compared with 10 days, a 5-day remdesivir course may reduce mortality and need for mechanical ventilation, and may increase recovery and/or clinical improvement by small to moderate amounts, and may reduce serious adverse events among patients not requiring mechanical ventilation at baseline. Drug costs would be lower. Pregnant women, children under age 12, and individuals with severe renal and hepatic dysfunction have been excluded from studies. Caution and monitoring are indicated if remdesivir is used in these individuals. The FDA notes that remdesivir side effects include elevated liver enzymes and allergic reactions (which may include changes in blood pressure and heart rate, low blood oxygen level, fever, shortness of breath, wheezing, swelling (eg, lips, around eyes, under the skin), rash, nausea, sweating, or shivering).9

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On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19). On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.2

On February 9, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2. They are both investigational drugs and are not currently approved for any indication.

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On February 25, 2021, FDA reissued the February 9, 2021 letter.³ On August 27, 2021, FDA reissued the February 25, 2021 letter.⁴

On September 16, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 27, 2021 letter in its entirety, to also authorize bamlanivimab and etesevimab administered together for emergency use as post-exposure prophylaxis in certain adults and pediatric individuals.

Based on the review of the data from the Phase 2/3 BLAZE-1 trial (NCT04427501), a randomized, double-blind, placebo-controlled clinical trial, and the Phase 2 BLAZE-4 trial (NCT04634409), a randomized, double-blind, placebo-controlled clinical trial, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and that, when used under the conditions described in this authorization, the known and potential benefits of bamlanivimab and etesevimab administered together outweigh the known and potential risks of such products.

Additionally, based on the review of the topline analysis of data from BLAZE-2 Part 1 (also known as Trial J2X-MC-PYAD; NCT04497987), a Phase 3 randomized, double-blind, placebocontrolled trial evaluating bamlanivimab alone for prevention of COVID-19 in residents and staff of skilled nursing facilities following a confirmed reported case of SARS-CoV-2 infection at the facility, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who

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U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020.

² U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).

are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under such conditions, the known and potential benefits of bamlanivimab and etesevimab outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of bamlanivimab and etesevimab administered together for treatment and as post-exposure prophylaxis of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

³ FDA revised the condition on instructional and educational materials. New conditions were also incorporated on the establishment of a process for monitoring genomic databases for the emergence of global viral variants of SARS-CoV-2 and the assessment, if requested by FDA, of the activity of the authorized bamlanivimab and etesevimab against any global SARS-CoV-2 variant(s) of interest.

⁴FDA revised the authorized use for bamlanivimab and etesevimab administered together clarifying the meaning of "severe COVID-19" and further limited the use of bamlanivimab and etesevimab by authorizing bamlanivimab and etesevimab administered together only in those states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%. Revisions were also incorporated to the conditions on compliance with cGMPs, product quality reporting, requests for CMC (chemistry, manufacturing and controls) changes to this authorization, the provision of samples of the authorized bamlanivimab and etesevimab to HHS, upon request, and the conditions on advertising and promotion.

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The randomized, double-blind, placebo-controlled trial – the gold standard for scientific research -evaluated the efficacy and safety of a 3-day course of remdesivir given through an IV in 562 nonhospitalized patients at high risk for severe COVID.

Remdesivir demonstrated an 87% reduction in risk for COVID-19-related hospitalization or death compared with the placebo group.

"These latest data show remdesivir's potential to help high-risk patients recover before they get sicker and stay out of the hospital altogether," cardiologist Robert L. Gottlieb, of Baylor University Medical Center in Houston, said in the press release. Gottleib was the lead investigator for the study.

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The oral medicine is called Paxloid. Similar to Merck's new pill that was approved in the U.K. on Thursday, Pfizer said its drug showed good results when administered within five days of the first COVID-19 symptoms.

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Compared to placebo (n=842), people who received a single dose of REGEN-COV (n=841) experienced:

• 81.6% reduced risk of developing COVID-19 during the pre-specified follow-up period, between months 2-8 (7 REGEN-COV, 38 placebo; 95% confidence interval [CI]: 59.8%, 91.6%; nominal p<0.0001).

- 81.5% reduced risk of developing COVID-19 at any time during the 8 months after receiving REGEN-COV (20 REGEN-COV, 108 placebo; 95% CI: 70.6%, 88.4%; nominal p<0.0001).
- During the 8-month assessment period, 0 individuals in the REGEN-COV group were hospitalized due to COVID-19, compared to 6 individuals in the placebo group (1 person in the first month; 5 people during months 2-8). There were no deaths due to COVID-19 in any treatment group during the 8-month assessment period, and there were no new safety signals identified for REGEN-COV.
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The Food and Drug Administration (FDA) approved an Investigational New Drug application for the trial. A central institutional review board (Advarra) reviewed and approved the trial protocol for all participating sites. (Advarra is a propriety company which on their internet listing are: Industry Experts—The Advarra Advantage: Our Expertise:

The Advarra advantage is built on our industry and domain expertise. Our experts are change agents and thought leaders with deep experience in clinical research. Together, we solve mission-critical challenges and bring life-changing therapies to participants faster. (Please note, Advarra's experts listed on their website https://www.advarra.com/about/industry-experts/ include NO MEDICAL CLINICIANS LIKE AN M.D. OR A D.O. In short, the SIREN-C3PO clinical trial NCT04355767 was reviewed by a proprietary company and NOT by any University School of Medicine IRB, any participating Hospital IRB, or the FDA's IRB directly.)

PLEASE note that the complete article and the supplementary appendix can be found:

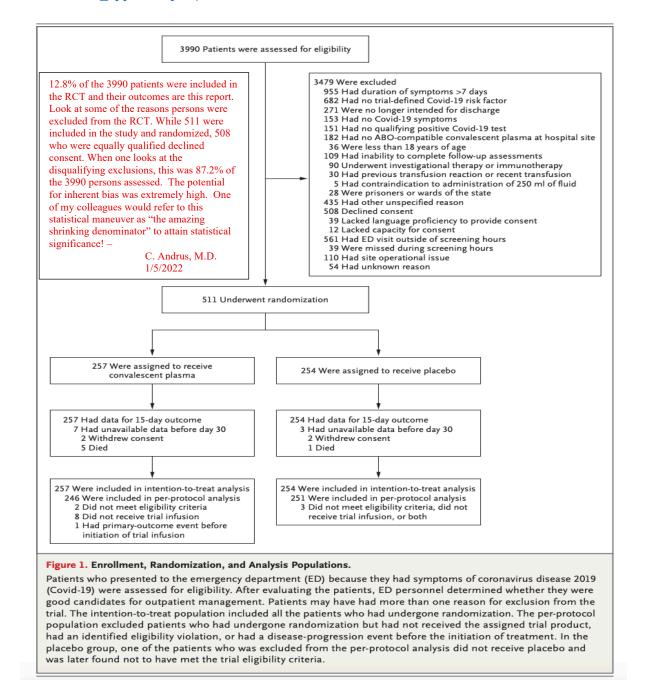
Korley FK, Durkalski-Maudin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, Kaplan A, Lowell E, et al., for the DIREN-C3PO Investigators*: Early convalescent plasma for high-risk outpatients with Covid-19. URL from article N Engl J Med 2021 Nov 18; 385: 1951-1960. https://www.nejm.org/doi/10.1056/NEJMoa2103784 This reference from the article is just an abbreviation; The full article is

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2103784?articleTools=true and the

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Supplementary Appendix which is very important can be found at (<a href="https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa210



In Figure 1. **Enrollment, Randomization, and Analysis Populations**, of the 3990 patients presenting to the Emergency Room, 3479 (87.2%) were excluded as listed in the box above. The number of eligible patients that refused to participate

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in this placebo RCT was 508 and with the 561 that presented outside of ED screening hours and thus were rejected. These two exclusion factors totaled over twice as many patients (1069) as were included in this study of 511. What is more, when the NIH announced the closure of this trial on March 2, 2021 never reaching its statistical-directed goal of 900 patients (minimum ß that the researchers agreed upon for a valid study), it proceeded to conclude that early administration of Passive Immunization via COVID-19 Convalescent Plasma (CCP) was not helpful. By excluding so many individuals, this study is probably a skewed, underpowered trial which the NIH and the editors of *The New England* Journal of Medicine should never have published.

It should also be noted that at the end of the author list on the front page of this article, it is stated: ...for the SIREN-C3PO Investigators* where the "*" refers to the statement in the right margin:

*A list of the SIREN-C3PO investigators is provided in the Supplementary Appendix, available at NEJM.org which is 20 pages long (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2103784/suppl_file/nejmoa210 3784 appendix.pdf) In this Supplementary Appendix major criteria for inclusion in the study changed from Protocol Version 1 of June 17, 2020 through Version 2 of July 2, 2020, Version 3 of September 7, 2020, Version 4 of November 3, 2020 to Version 5, February 16, 2021:

Has at least one study defined risk factor for severe COVID-19 illness:

Age ≥ 50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression

Yet, in Table 1. Characteristics of the Patients at Baseline:

Characteristic	Convalescent Plasma	Placebo
	(N=257)	(N=254)
Median age (IQR)	54 (42-62)	54 (40-62)

there were patients of 42-49 years in the Convalescent Plasma group and patients of 40-49 years in the placebo group. Those patients should have been excluded due to their "youngness" that violated the stated inclusion criteria of all five Protocol versions of this trial. Were the SIREN-C3PO investigators, the NIH, and the editors of The New England Journal of Medicine being truthful to the American public? Has this paper done a disservice to the American public and to the World? As the NEJM attests to the participattion in the *International* Committee of Medical Journal Editors (ICMJE), they owe the American people an independent (independent from the U.S. Government and The New England Journal of Medicine) peer review of this paper with regards to appropriateness: Simply put, can this paper even conclude that which it concludes? ----- May 30, 2022 -----

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of America (U.S.A.), the World, and specifically the President of the U.S.A. without any compensation to the author. All submissions including this timeline bibliography can be obtained under the Freedom of Information Act (FOIA) by formally requesting a copy of NIAID Case #12276 from the FIOA Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

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- **1023)** 2021-11-18 CBS Interactive Inc.: Frozen vials marked "Smallpox" found in lab freezer in Pennsylvania, CDC says. https://www.cbsnews.com/news/smallpox-vials-lab-freezer-pennsylvania-cdc/
- **1024)** 2021-11-18 Picchi A: OSHA is suspending enforcement of the government's new employer vaccine rule. https://www.cbsnews.com/news/covid-vaccine-mandate-osha-suspending-enforcement/
- 1025) 2021-11-18 Kimball S: Biden administration buys \$10 million courses of Pfizer Covid treatment pill in \$5 billion deal. https://www.cnbc.com/2021/11/18/biden-administration-buys-10-million-courses-of-pfizer-covid-treatment-pill.html
- 1026) 2021-11-19 Collin L: Upper Midwest faces spike in COVID-19 infections: "It's unprecedented." CBS Evening News, November 19, 2021. https://www.cbsnews.com/news/covid-19-upper-midwest-minnesota-spike/
- 1027) 2021-11-19 CBS News: U.S. Scientist says he's found the real COVID patient zero, and "strong evidence" pandemic started at animal market. CBS News, November 19, 2021. https://www.cbsnews.com/news/origin-covid-19-us-scientist-patient-zero-wuhan-china-evidence-market/
- 1028) 2021-11-19 FDA: FDA NEWS RELEASE: Coronavirus (COVID-19) Update: FDA expands eligibility for COVID-19 Vaccine boosters. November 19, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-covid-19-vaccine-boosters
- 1029) 2021-11-19 Tin A: CDC authorizes COVID vaccine boosters for all adults. CBS News, November 19, 2021. https://www.cbsnews.com/news/covid-vaccine-booster-shot-cdc-fda-authorization/
- 1030) 2021-11-21 The Tabernacle Choir at Temple Square: November 21, 2021 #4810 Music & the Spoken Word. (This played on KMOX radio, St. Louis, MO at 6:00 a.m. while on my way to the St. Louis (John Cochran division) VAMC to round on the Veteran patients of General Surgery II. Listening to this message epitomized that of which the concept of gratitude of Thanksgiving Day is engendered and our assurance by the Constitution and the Bill of Rights of our freedoms of which we all-to-often take for granted.)
 https://www.thetabernaclechoir.org/videos/november-21-2021-4810-music-and-the-spoken-word.html
- **1031)** 2021-11-21 Fauci A: Fauci says he'd be "astounded" if there wasn't an autopsy on what went wrong in COVID response, CBS News. (Attempt of accessing this website on Google: Fauci Brennan *Face the Nation* on November 22, 2021 was unsuccessful but "autopsy"

provided by yahoo): https://www.yahoo.com/now/fauci-says-hed-astounded-wasnt-150638991.html

> Margaret Brennan: Why aren't we having a national conversation about what went wrong? I mean, apart from this room right now, why isn't there a 9/11-type commission?

Anthony Fauci, M.D.: Yeah. I think what's going to happen is that you are going to see that for sure, Margaret. I think the lack of doing that now is because you're focusing on getting this thing under control. I would be astounded if we didn't have a very serious look at what went right, what went wrong, from a public health standpoint, from a local standpoint, from a global standpoint. I don't think that the public should imagine that this is going to go through—with already 760,000 Americans dying, and 40 plus million, at least, being infected. Close to 6 million people globally dying—and we're not going to look back at this and tear it apart, examine it, do an autopsy on it and try and figure out [AUDIO OUT]...

WHEN the Wayback Machine (Internet Archive) was accessed November 22, 2021 of the only capture for the Yahoo version of Face the Nation of Nov 21, 2021: https://web.archive.org/web/20211121161530/https://www.yahoo.com/now/fauci-sayshed-astounded-wasnt-150638991.html yielded:

yahoo!

CBS News: Fauci says he'd be "astounded" if there wasn't an autopsy on what went wrong in COVID response" Sun, November 21, 2021, 4:06 PM –Dr. Anthony Fauci tells Margaret Brennan in a wide-ranging conversation that he expects a full investigation into what went wrong in the Coronavirus response.

BUT THE ACTUAL INTERVIEW CANNOT BE OPENED stating: Cannot Plav Video—Due to license restrictions; this video can only be viewed on Yahoo. RS-100-204.

WHEN on November 23, 2021, the Google attempt at searching: "Fauci Brennan Face the Nation" failed, searching for "Fauci Brennan Sixty Minutes" yielded the official CBS News website:

https://www.cbsnews.com/video/fauci-says-hed-be-astounded-if-there-wasnt-anautopsy-on-what-went-wrong-in-covid-response/#x

-- May 30, 2022 -----

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Margaret Brennan: It's been almost two years since a mysterious virus began circulating in Wuhan, China. And there are still far more questions than answers about where it came from and how we can prepare for the next pandemic. For our broadcast Sunday we talked with Dr. Anthony Fauci to get his thoughts on just some of those questions. Here's a preview:

Margaret Brennan: Why aren't we having a national conversation about what went wrong? I mean, apart from this room right now, why isn't there a 9/11-type commission?

Anthony Fauci, M.D.: Yeah. I think what's going to happen is that you are going to see that for sure, Margaret. I think the lack of doing that now is because you're focusing on getting this thing under control. I would be astounded if we didn't have a very serious look at what went right, what went wrong, from a public health standpoint, from a local standpoint, from a global standpoint. I don't think that the public should imagine that this is going to go through—with already 760,000 Americans dying, and 40 plus million, at least, being infected. Close to 6 million people globally dying—and we're not going to look back at this and tear it apart, examine it, do an autopsy on it and try and figure out.

Margaret Brennan: Dr. Anthony Fauci coming up Sunday on Face the Nation.

When the web.archive using the official CBS New URL site above, Margaret Brennan video appears speaking without sound and when the arrow is the screen becomes black with a white circle spiraling in the center. The caption underneath reads: Fauci says he'd be "astounded" if there wasn't an autopsy on what went wrong in COVID response. Dr. Anthony Fauci tells Margaret Brennan in a wideranging conversation that he expects a full investigation into what went wrong in the Coronavirus response.

https://web.archive.org/web/20211121152005/https://www.cbsnews.com/video/fauci-says-hed-be-astounded-if-there-wasnt-an-autopsy-on-what-went-wrong-incovid-response/

- 1032) 2021-11-19 KFF-Henry J Kaiser Family Foundation: Status of State Medicaid Expansion Decisions: Interactive Map. https://www.kff.org/medicaid/issue-brief/status-of-state-medicaid-expansion-decisions-interactive-map/
- **1033)** 2021-11-19, last updated: Boston National Historical Park: Smallpox, Inoculation, and the Revolutionary War. https://www.nps.gov/articles/000/smallpox-inoculation-revolutionary-war.htm

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1034) 2021-11-23 Trump D, Jr: @DonaldJTrumpJr

https://twitter.com/DonaldJTrumpJr/status/1463366937065390085/photo/1

https://web.archive.org/web/20211124215038/https://twitter.com/DonaldJTrumpJr/status/1463366937065390085/photo/1

1035) 2021-11-23 CBS News: Full transcript of "Face the Nation" on November 21, 2021. "On this "Face the Nation" broadcast moderated by Margaret Brenna:" The transcript has yet to be released but nowhere in the titles is Dr. Anthony Fauci listed.

Sen. Kirsten Gillibrand, (D-NY)

Sen. Ted Cruz, (R-TX)

Derrick Johnson, President and CEO, NAACP

Dr. Scott Gottlieb, Former FDA Commissioner

Anthony Salvanto, CBS News Elections & Surveys Director

 $\underline{https://web.archive.org/web/20211121192431/https://www.cbsnews.com/news/full-transcript-of-face-the-nation-on-november-21-2021/$

1036) 2021-11-28 Fauci A, Brennan M: Transcript: Dr. Anthony Fauci on "Face the Nation," November 28, 2021. CBS NEWS, Face the Nation, 2021 November 28, 2021, 7:21 AM https://www.cbsnews.com/news/transcript-dr-anthony-fauci-on-face-the-nation-november-28-2021/

Please note that the statement regarding autopsy was edited out from the discussion that aired on Sunday morning Face the Nation on November 28, 2021 on the St. Louis affiliate KMOV:

DR. FAUCI: Yeah, I think what's going to happen is that you are going to see that for sure, MARGARET. I think the lack of doing that now is because you're focusing on getting this thing under control. I would be astounded if we didn't have a very serious look at what went right, what went wrong, from a public health standpoint, from a local standpoint, from a global standpoint. I don't think that the public should imagine that this is going to go through with already 760,000 Americans dying and 40 plus million at least being infected, close to six million people globally dying. And we're not going to look back at this and tear it apart, examine it, do an autopsy on it and try and figure out. So people should not think that that's not going to happen. It's not happening now because everybody's focusing on getting this thing under control.

1037) 2021-11-28 Bice A: Fauci: 'I'm going to be saving lives and they're going to be lying.' POLITICO https://www.politico.com/news/2021/11/28/fauci-lying-covid-research-cruz-523412

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- **1038)** 2021-11-29 Kimball S: Pfizer CEO confident Covid treatment pill will be effective against omicron variant. https://www.cnbc.com/2021/11/29/pfizer-ceo-confident-covid-treatment-pill-effective-against-omicron-variant.html
- 1039) 2021-12 Personalis, Inc.: Veterans Health Administration 75 Years: *A legacy of service. The future of care.* Personalis, Inc., 1330 O'Brien Drive, Menlo Park, CA. 94025. www.personalis.com wrightusa.com, page 20.
- **1040)** 2021-12-01 Lederer EM: Fauci says COVID diverted resources from fighting AIDS. https://www.aol.com/news/fauci-says-covid-diverted-resources-035825200-153355420.html
- **1041)** 2021-12-02. Weinrech DM and Others: *e*81 REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. D.M. Weinreich and Others.

2021-09-29 Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Xiao J, Hooper AT, Hamilton JD, Musser BJ, Rofail D, Hussein M, Im J, Atmodjo DY, Perry C, Pan C, Mahmood A, Hosain R, Davis JD, Turner KC, Baum A, Kyratsous CA, Kim Y, Kampman W, Roque-Guerrero L, Acloque G, Aazami H, Cannon K, Simon-Campos, Bocchini JA, Kowal B, DiCioccio AT, Soo Y, Geba GP, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, for the Trial Investigators*: REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med posted on NEJM.org on September 29, 2021. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2108163?articleTools=truewith the "*" which is the complete article: https://www.nejm.org/doi/full/10.1056/NEJMoa2108163 of September 29, 2021.

On the hardcopy version of this paper is noted in the front page index of *The New England Journal of Medicine*, 2021 December 2; 385 (23), front page INDEX:

e81 REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. D.M. Weinreich and Others but the article is not in this hardcopy but in the electronic format only:

<u>https://www.nejm.org/doi/full/10.1056/NEJMoa2108163</u> and for the entire supplement:

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2108163/suppl_file/nejmoa2108163_appendix.pdf

1042) 2021-12-02 Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, Grinberg T, Auster O, Dagan N, Balicer RD, Kornowski R: Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med 2021 December 2; 385 (23): 2132-2139. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110737?articleTools=true

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- https://www.nejm.org/doi/full/10.1056/NEJMoa2110737 which is the electronic version published on October 6, 2021.
- 1043) 2021-12-02 Mevorach D, Anis E, Cedar N, Bromberg M, Nadir E, Olsha-Castell S, Arad D, Hasin T. Levi N, Amir O, Meir K, Cohen D, Dichtiar R, Novick D, Hershkovitz Y, Dagan R, Leitersdorf I, Ben-Ami R, Miskin I, Saliba W, Muhsen K, Levi Y, Green MS, Keinan-Boker L, Alroy-Preis S: Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Isreal. N Engl J Med 2021 December 2; 385 (23): 2140-2149. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2109730
- **1044)** 2021-12-02 Caforio ALP: Receipt of mRNA Vaccine against Covid-19 and myocarditis. N Engl J Med 2021 December 2; 385 (23): 2189-2190. https://www.nejm.org/doi/pdf/10.1056/NEJMe2116493?articleTools=true
- 1045) 2021-12-02 Chutel L, Pénza-Peña R: Prior infection is little defense against virus variant, scientists say. Evidence from South Africa, where the Omicron variant already dominates, shows a high rate of reinfection of people who have already had the coronavirus. The New York Times https://www.nytimes.com/2021/12/02/world/africa/virus-omicronvariant-reinfection.html
- 1046) 2021-12-03 Albert V, Tin A: Omicron COVID-19 variant detected in 5 states, a day after first case was reported in U.S. CBS News https://www.cbsnews.com/news/omicron-variantcovid-19-cases-detected-united-states/
- **1047)** 2021-12-03 FDA: FDA expands authorization of two monoclonal antibodies for treatment and post-exposure prevention of COVID-19 to younger pediatric patients, including newborns. U.S. Food and Drug Administration News Release. https://www.fda.gov/news-events/press-announcements/fda-expands-authorization-twomonoclonal-antibodies-treatment-and-post-exposure-prevention-covid-19

PLEASE NOTE:

Mr. President, the actual EUA regarding this FDA News Release was based on the EUA letter by RADM Denise M. Hinton, R.N., M.S., F.D.A. Chief Scientist, on September 16, 2021. Mr. President, over the last 18 months, RADM Hinton has issued FDA EUAs regarding Passive Immunization agents like COVID-19 Convalescent Plasma; Monoclonal Antibodies and Antibody Cocktails, etc. because that is her job. She has walked the straight and narrow in responsibly issuing these EUAs for the last 18 months for that is her job; and she has done it admirably! In those introductory discussions of each of the EUAs she has laid out the evolutionary histories of these drugs and biologic agents and the justifications and directions on how to clinically administer them. Unfortunately, every EUA continues the status of the drug or biologic as *Investigational (Experimental)*. What does that mean? – It means that clinically a physician has to apply for an

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individual FDA Investigational New Drug (IND) application every time he/she has a patient who has contracted COVID-19 and administration of the drug or biologic is indicated.

The FDA tried to circumvent the need for individual physicians requesting individual INDs for individual patients regarding COVID-19 Convalescent Plasma from March 24, 2020 until August 23, 2020 by issuing an Expanded Access authorization. An expanded access authorization is by FDA/NIH definition "compassionate" use - providing an Investigational Drug given off protocol with the stipulation that any outcome data cannot be used to generate any prospective research information.

- 1048) 2021-12-03 Lilly: Lilly's bamlanivimab with etesevimab authorized as the first and only neutralizing antibody for emergency use in COVID-19 patients under the age of 12. https://investor.lilly.com/node/46306/pdf
- **1049)** 2021-12-03 Enago Academy: Quick guide to biostatistics in clinical research: Hypothesis testing. https://www.enago.com/academy/quick-guide-to-biostatistics-inclinical-research-hypothesis-testing/
 - 2021-01-22 Enago Academy: A quick guide to clinical trials (Part 1: An Overview). https://www.enago.com/academy/a-quick-guide-to-clinical-trials-part-1-an-overview/
 - 2018-05-23 Enago Academy: A quick guide to clinical trials (Part 2: The Process). https://www.enago.com/academy/a-quick-guide-to-clinical-trials-part-2-the-process/
- 1050) 2021-12-06 wcg FDANEWS: FDA updates EUA for Eli Lilly's COVID-19 antibody cocktail to include young children. https://www.fdanews.com/articles/205656-fda-updateseua-for-eli-lillys-covid-19-antibody-cocktail-to-include-young-children
- 1051) 2021-12-07 World Health Organization: WHO recommends against the use of convalescent plasma to treat COVID-19. December 7, 2021. https://www.who.int/news/item/07-12-2021-who-recommends-against-the-use-ofconvalescent-plasma-to-treat-covid-19#:~:text=Convalescent%20plasma%20is%20a%20transfusion,while%20it%20has%20sign ificant%20costs
- 1052) 2021-12-08 Kimball S: Pfizer will submit full data on Covid treatment pill to the FDA in a few days, CEO says. CNBC PRO Dec 8, 20212. https://www.cnbc.com/2021/12/08/pfizerwill-submit-full-data-on-covid-treatment-pill-to-the-fda-in-a-few-days-ceo-says.html
- 1053) 2021-12-08 FDA News Release: Coronavirus (COVID-19) Update: FDA authorizes new long-acting monoclonal antibodies for pre-exposure prevention of COVID-19 in certain individuals. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-

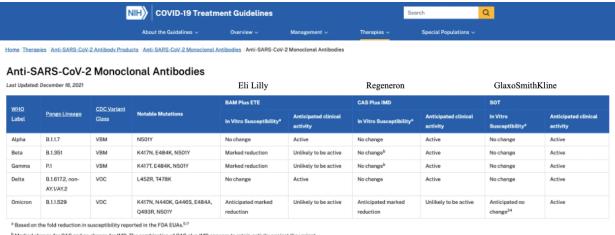
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update-fda-authorizes-new-long-acting-monoclonal-antibodies-preexposure#:~:text=Today%2C%20the%20U.S.%20Food%20and,years%20of%20age%20and %20older Per an e-mail of February 18, 2022, 1:31 PM from the Deputy Chief of Staff— John Cochran Division, VA St. Louis Health Care System: The St. Louis VA has received a very limited supply of Evusheld for initial distribution. The Scarce Resource Team has planned an allocation method to maximize the ethical principles of respect, consistency, stewardship, transparency, and equity.

- 1054) 2021-12-08 Jimenez D: Covid-19: GSK's sotrovimab retains activity against Omicron variant. Pharmaceutical Technology. https://www.pharmaceutical-technology.com/special- focus/covid-19/covid-19-gsk-sotrovimab-activity-omicronvariant/#:~:text=GlaxoSmithKline%20(GSK)%20and%20Vir%20Biotechnology,%2DCoV% 2D2%20variant%20Omicron.
- 1055) 2021-12-08 NIH / NIAID: COVID-19 single-dose nasal vaccine designed for infants, children. https://www.niaid.nih.gov/news-events/covid-19-single-dose-nasal-vaccine
- 1056) 2021-12-13 Supreme Court of the U.S.: JOSEPH R. BIDEN, Jr, PRESIDENT OF THE UNITED STATES, et al., APPLICANTS 21A240 v. MISSOURI, et al. and XAVIER BECERRA, SECRETARY OF HEALTH AND HUMAN SERVICES, et al APPLICANTS 21A241 v. LOUISANA, et al. on applications for stays. https://www.supremecourt.gov/opinions/21pdf/21a240 d18e.pdf
- 1057) 2021-12-16 AstraZeneca: EVUSHELD long-acting antibody combination retains neutralizing activity antibody combination retains neutralizing activity against Omicron variant in independent FDA study. https://www.astrazeneca-us.com/media/pressreleases/2021/evusheld-long-acting-antibody-combination-retains-neutralizing-activityagainst-omicron-variant-in-independent-fda-study.html
- **1058)** 2021-12-16 NIH: COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibodyproducts/anti-sars-cov-2-monoclonal-antibodies/
- 1059) 2021-12-16 NIH: Anti-SARS-CoV-2 Monoclonal Antibodies. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibodyproducts/anti-sars-cov-2-monoclonal-antibodies/
- 1060) 2021-12-16 NIH: Anti-SARS-CoV-2 Monoclonal Antibodies, Table A. (Last updated 16, 2021) https://www.covid19treatmentguidelines.nih.gov/tables/table-a/ According to the Wayback Machine there are digital copies of updates going back to August 6, 2021 with the NIH "last update" is August 4, 2021.

https://web.archive.org/web/20210806205833/https://www.covid19treatmentguidelines.nih.g ov/tables/table-a/

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b Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity ag

Kev: BAM = bamlanivimab: CAS = casirivimab: CDC = Centers for Disease Control and Prevention: ETE = etesevimab; EUA = Emergency Use Authorization: FDA = Food and Drug Administration: IMD = imdevimab; SOT = so onitored; VOC = variant of concern; WHO = World Health Organization

1061) 2021-12-16 CDC: CDC endorses ACIP's updated COVID-19 vaccine recommendations. https://www.cdc.gov/media/releases/2021/s1216-covid-19-vaccines.html

> Today, CDC is endorsing updated recommendations made by the Advisory Committee on Immunization Practices (ACIP) for the prevention of COVID-19, expressing a clinical preference for individuals to receive an mRNA COVID-19 vaccine over Johnson & Johnson's COVID-19 vaccine. ACIP's unanimous recommendation followed a robust discussion of the latest evidence on vaccine effectiveness, vaccine safety and rare adverse events, and consideration of the U.S. vaccine supply. The U.S. supply of mRNA vaccines is abundant – with nearly 100 million doses in the field for immediate use. This updated CDC recommendation follows similar recommendations from other countries, including Canada and the United Kingdom. Given the current state of the pandemic both here and around the world, the ACIP reaffirmed that receiving any vaccine is better than being unvaccinated. Individuals who are unable or unwilling to receive an mRNA vaccine will continue to have access to Johnson & Johnson's COVID-19 vaccine.

- 1062) 2021-12-17 Cooper R: Noble lies are a public health hazard. THE WEEK, 17 Dec 2021. https://theweek.com/coronavirus/1008155/noble-lies-are-a-public-health-hazard
- **1063)** 2021-12-19 LaPook J: COVID and safer holiday gatherings, 11:10 -14:57 https://www.cbs.com/shows/cbs-sundaymorning/video/ztOo3TeLHgxraEUXbeOmcDfzIn7BYZCX/-sunday-morning-full-episode-12-19/
- **1064)** 2021-12-19 Braver R: Dr. Francis Collins retires as NIH Director, 15:01 22:38, CBS News https://www.cbsnews.com/video/retiring-nih-director-dr-francis-collins/
- 1065) 2021-12-19 Collins F: Transcript: NIH Director Dr. Francis Collins on "Face the Nation," December 19, 2021. CBSNews https://www.cbsnews.com/news/transcript-nih-director-drfrancis-collins-face-the-nation-12-19-2021/

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- 1066) 2021-12-19 Dellatto M: Fauci: Pfizer's possibly game-changing Covid-19 pill won't be widely available for 'months."

 https://www.forbes.com/sites/marisadellatto/2021/12/19/fauci-pfizers-possibly-game-changing-covid-19-pill-wont-be-widely-available-for-months/?sh=1bc7e423cc30
- 1067) 2021-12-20 Senefeld JW, Johnson PW, Kunze KL, Bloch EM, van Helmond N, Golafshar MA, Klassen SA, Klompas AM, Sexton MA, Diaz Soto JC, Grossman BJ, Tobian AAR, Goel R, Wiggins CC, Bruno KA, van Buskirk CM, Stubbs JR, Petersen MM, Sachais BS, Buras MS, Wieczorek MA, Russoniello B, Dumont LJ, Baker SE, Vassallo RR, Shepherd JRA, Young PP, Verdun NC, Marks P, Haley NR, Katz L, Herasevich V, Waxman DA, Whelan ER, Bergman A, Clayburn AJ, Grabowski MK, Larson KF, Ripoll JG, Andersen KJ, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Blair JE, Buchholtz ZA, Pletsch MC, Wright K, Greenshields JT, Joyner MJ, Wright RS, Carter RE, Fairweather DL: Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national registry study. PLOS Medicine 2021 December 20; 1-28. https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003872
- 1068) 2021-12-20 O'Shaunghnessy JA: FDA EUA regarding AstraZemeca Pharmaceuticals LP's EVUSHELD for use as pre-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals... Tixagevimab and Cilgavimab, the active components of EVUSHELD, are neutralizing IgG1 monoclonal antibodies that bind to distinct, non-overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2. EVUSHELD is an investigational drug and is not approved for any uses, including use as pre-exposure prophylaxis of COVID-19. https://www.fda.gov/media/154704/download
- **1069)** 2021-12-21 Kozlov M: Omicron overpowers key COVID antibody treatments in early tests—Nearly all of the monoclonal antibodies used to prevent severe disease fail to stand up to the new variant, laboratory assays show. https://www.nature.com/articles/d41586-021-03829-0
- 1070) 2021-12-21 Sullivan DJ, Gebo KA, Shoham S, Bloch EM, Lau B, Shenoy AG, Mosnaim GS, Gniadek TJ, Fukuta Y, Patel B, Heath SL, Levine AC, Meisenberg BR, Spivak ES, Anjan S, Huaman MA, Blair JE, Currier JS, Paxton JH, Gerber JM, Petrini JR, Broderick PB, Rausch W, Cordisco ME, Hammel J, Greenblatt B, Cluzet VC, Cruser D, Oei K, Abinante M, Hammitt LL, Sutcliffe CG, Forthal DN, Zand MS, Cachay ER, Raval JS, Kassaye SG, Foster EC, Roth M, Marshall CE, Yarava A, Lane K, McBee NA, Gawad AL, Karlen N, Singh A, Ford DE, Jabs DA, Appel LJ, Shade DM, Ehrhardt S, Baksh SN, Laeyendecker O, Pekosz A, Klein SL, Casadevall A, Tobian AAR, Hanley DF: Randomized controlled trial of early outpatient COVID-19 treatment with high-titer.

 https://www.medrxiv.org/content/10.1101/2021.12.10.21267485v1.full.pdf
- **1071)** 2021-12-22 FDA: Coronavirus (COVID-19) Update: FDA authorizes first oral antiviral for treatment of COVID-19. https://www.fda.gov/news-events/press-

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announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19

1072) 2021-12-22 O'Shaughnessy JA, acting FDA Chief Scientist: To Eli Lilly and Company. RE: Emergency Use Authorization 094. U.S. Food and Drug Administration. https://web.archive.org/web/20211224034648/https://www.fda.gov/media/145801/download

On December 22, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the December 3, 2021 letter in its entirety, to remove the limitation on the authorized use of bamlanivimab and etesevimab that previously authorized bamlanivimab and etesevimab administered together only in those states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%. FDA is also revising the healthcare provider fact sheet to remove this limitation on the authorized use of bamlanivimab and etesevimab and to incorporate additional virology information.

https://www.fda.gov/media/145801/download January 24, 2022.

https://www.fda.gov/media/156151/download February 11, 2022

https://www.fda.gov/media/143602/download Revoked March 2, 2021

2022-05-04 ASPR Office of the Assistant Secretary for Preparedness & Response: Important Bamlanivimab/Etesevimab Updates. https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Bamlanivimab-etesevimab/Pages/default.aspx

1073) 2021-12-22 Kavanaugh: Miscellaneous Order (12/22/2021) for oral arguments before the U.S. Supreme Court on Friday, January 7, 2022 in application 21A244: NAT. FED'N OF INDEP. BUS., ET AL. V. DEPT. OF LABOR, OSHA, ET AL. and application 21A247: OHIO, ET AL. V. DEPT. OF LABOR, ET AL. https://www.supremecourt.gov/orders/courtorders/122221zr2 f20h.pdf

1074) 2021-12-22 Barnes R: Supreme Court sets special hearing for Biden's vaccine rules for health-care workers, private businesses. The Washington Post.
https://www.washingtonpost.com/politics/courts_law/biden-vaccine-mandates-supreme-court/2021/12/22/dd3bab94-6382-11ec-a7e8-3a8455b71fad story.html

1075) 2021-12-22 Judith Dawson judith.dawson@bjc

Subject: 12/22/21 COVID-19 Communications to Providers

Being sent to active Medical Staff, Midlevel Providers and Office Managers:

mAB Clinic Updates:

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

accepting adult patients for post-exposure prophylaxis at this time. For information on eligibility and ordering, please visit. www.bjc.org/for-physicians/mab

Expanded EUA Criteria: Based on expanded EUA criteria, BJC HealthCare and Washington University are now able to offer monoclonal antibody therapy (mAb) to patients 0-11 years old. On Monday, December 20, 2021, St. Louis Children's Hospital began treating high-risk pediatric patients of all ages at the mAb clinic on the Washington University School of Medicine Campus as well as at the St. Louis Children's Specialty Care Center (CSCC) – South County. Please visit www.bjc.org/For-Physicians/mab for ordering information. ...

1076) 2021-12-22 O'Shaughnessy: FDA: EUA 105 letter to Pfizer regarding PAXLOID [nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentration to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOID is not approved for any use, including treatment of COVID-19.] https://web.archive.org/web/20211222180424/https://www.fda.gov/media/155049/download

PAXLOVID is comprised of nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOVID is not approved for any use, including for use for the treatment of COVID-19.

https://www.fda.gov/media/155049/download (2022-04-14)

This letter is in response to Pfizer, Inc.'s (Pfizer) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID (nirmatrelvir co-packaged with ritonavir) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3). On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19). 1 On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.2 PAXLOVID is comprised of nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, copackaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOVID is not approved for any use, including for use for the treatment of COVID-19. Based on the totality of scientific evidence available to FDA, including data from the clinical trial EPIC-HR (NCT04960202), a Phase 2/3 randomized, double blind, placebo-controlled clinical trial, it is reasonable to believe that ----- May 30, 2022 -----

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing

U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020. U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).

at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product. Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of PAXLOVID for the treatment of mildtomoderate COVID-19 in certain adults and pediatric patients, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

- 1077) 2021-12-22 Associated Press: Experts warn of 'perfect storm' in Missouri as cases jump. KSHB news. https://www.kshb.com/news/coronavirus/experts-warn-of-perfect-storm-inmissouri-as-cases-jump
- 1078) 2021-12-22 Gilead: Gilead announces New England Journal of Medicine publication of data demonstrating Veklury (Remdesivir) significantly reduced risk of hospitalization in high-risk patients with COVID-19. –Subgroup analyses show consistently high efficacy for patients regardless of underlying medical conditions associated with higher risk for severe COVID-19 compared with placebo-- https://www.gilead.com/news-and-press/press- room/press-releases/2021/12/gilead-announces-new-england-journal-of-medicinepublication-of-data-demonstrating-veklury-remdesivir-significantly-reduced-risk-ofhospitalization
- 1079) 2021-12-23 Thomas K, Robbins R: Covid antibody drugs go unused as need soars. The New York Times. https://web.archive.org/web/20201223152514/https://www.nytimes.com/2020/12/23/health/c ovid-antibody-treatment.html
- 1080) 2021-12-23 Haseltine WA: Omicron evades most but fortunately not all monoclonal antibodies. Forbes Healthcare https://www.forbes.com/sites/williamhaseltine/2021/12/23/omicron-evades-most-butfortunately-not-all-monoclonal-antibodies/?sh=fecdf6082fec
- **1081)** 2021-12-23 O'Shaughnessy JA: EUA Letter 108 to Merck to authorize molnupiravir (a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis). https://web.archive.org/web/20211223145523/https://www.fda.gov/media/155053/download

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- 1082) 2021-12-23. Tin A: FDA authorizes second COVID antiviral pill, from Merck, if no alternatives available. https://www.cbsnews.com/news/fda-authorizes-covid-antiviral-pillmerck-molnupiravir/#
- 1083) 2021-12-23 FDA: Coronavirus (COVID-19) Update: FDA Authorizes additional oral antiviral for treatment of COVID-19 in certain adults. https://www.fda.gov/newsevents/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oralantiviral-treatment-covid-19-certain
- 1084) 2021-12-23 Quinn M: Supreme Court to hear challenges to Biden COVID-19 vaccine rules for health care workers, large companies. CBS NEWS https://www.cbsnews.com/news/supreme-court-biden-covid-19-vaccine-rules-health-careworkers-large-companies/
- 1085) 2021-12-23 Ellis R: Monoclonal antibody for Omicron in short supply. WEBMD news brief. https://www.webmd.com/lung/news/20211222/monoclonal-antibody-for-omicron-inshort-supply
- **1086)** 2021-12-23 Minnesota Department of Health: Ethical framework for allocation of Monoclonal Antibodies during the COVID-19 Pandemic. https://web.archive.org/web/20211224142017/https://www.health.state.mn.us/diseases/coron avirus/hcp/mabethical.pdf

This framework has been updated since 11/12/21 to clarify allocation priorities, clinical prioritization, potential for deprioritization of access for post-exposure prophylaxis (PEP) patients, and lottery considerations.

Introduction

Since November 2020, the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) to permit the emergency use of investigational monoclonal antibody (mAb) therapies for the treatment of mild to moderate COVID-19 in adult and pediatric patients. The currently authorized mAbs are:

- Casirivimab/imdevimab (Regeneron) EUA issued Nov. 21, 20201
- Bamlanivimab/etesevimab (Eli Lilly) EUA issued Feb. 9, 20212
- Sotrovimab (GlaxoSmithKline LLC) EUA issued Oct. 8, 20213

The FDA issued an EUA on Nov. 9 for the use of bamlanivimab alone for treatment of COVID-19. 2020. 4 As of April 16, 2021; however, this EUA has been revoked. 5 This revocation was issued due to concerns about the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone, resulting in the increased risk for

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treatment failure. The FDA therefore determined that the known and potential benefits of bamlaniyimab, when administered alone, no longer outweigh the known and potential risks for its authorized use.

In May and June of 2021, the FDA issued updated eligibility criteria for mAb treatment for both casirivimab/imdevimab (Regeneron) and bamlanivimab/etesevimab, and authorized the addition of a $subcutaneous\ route\ of\ administration\ for\ casirivimab/imdevimab\ (Regeneron)\ as\ an\ alternative\ when\ intravenous\ and\ alternative\ alternative\ when\ alternative\ and\ alternative\ alternative\ when\ alternative\ and\ alternative\ alternative\ alternative\ al$ infusion is not feasible and would lead to delay in treatment.6

On July 30, 2021, the FDA updated the EUA for casirivimab/imdevimab (Regeneron) to authorize use of this product for post-exposure prophylaxis (PEP) in some patients. 7 On Sept. 16, 2021, the FDA updated the EUA for bamlanivimab/etesevimab to authorize use of this product for PEP in the same patient population as that for PEP using the Regeneron product, and with specific guidance that bamlanivimab/etesevimab would only be authorized for continued use in states where prevalent COVID-19 variants are susceptible to the mAb.8

With respect to treatment uses, the FDA has noted in the EUAs for the currently authorized mAbs:

"Based on the totality of scientific evidence available to FDA, it is reasonable to believe that..." these monoclonal antibody therapies "... may be effective in treating mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age or older weighing at least 40kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and that, when used under the conditions described in this authorization, the known and potential benefits ... when used to treat COVID-19 in such patients outweigh the known and potential risks of such product(s)."

The patient eligibility criteria listed in the EUA for the authorization of each of the currently authorized monoclonal antibody therapies are identical. For that reason, this document covers each of these therapies under the umbrella term "mAb." Notably, these mAbs are not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. The U.S. government has secured supplies of these investigational antibody therapies for distribution to states. Infusion facilities may order directly from the U.S. Department of Health and Human Services as needed.

Allocation and administration of these mAbs for treatment are time-sensitive, as the EUA for each specifies that infusions be administered as soon as possible after a positive COVID-19 test result and within 10 days of

 $\textbf{symptom} \, \textbf{onset.}^{10,11} \, \textbf{Consequently, communicating to health care systems, physicians, patients, and COVID-19}$ test sites the importance of rapid testing and referral for potential infusion is crucial. The EUA Fact Sheet states: "For treatment, intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment."12

For post-exposure prophylaxis (PEP) uses, the FDA notes:

"[I]t is reasonable to believe that [the authorized mAbs] may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under [such condition]s, the known and $potential\,benefits\,of\,[the\,authorized\,mAbs]\,\,outweigh\,the\,known\,\,and\,\,potential\,risks\,\,of\,such\,\,products."^{13}$

Allocation and administration of mAbs for PEP are also time-sensitive. The EUA states that mAbs should be administered for PEP "as soon as possible following exposure to SARS-CoV-2," without providing a more specific timeframe. 11 This framework recommends administering mAbs for PEP within 10 days from exposure for eligible patients who are not expected to mount an adequate immune response – e.g., those with immunocompromising conditions or on immunosuppressive medications – and administering mAbs for PEP within five days from exposure for all other eligible patients. Thus, communicating to health care systems, physicians, and relevant groups of patients about the option of accessing mAbs for PEP is crucial. For PEP, mAbs may be administered either via infusion or subcutaneous injection. $^{\rm 12}$

On Sept. 3, 2021, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel issued guidance outlining clinical prioritization when there is insufficient capacity to meet need for mAbs. 14 MCEC recommends a somewhat different approach to allocation in scarcity, which is outlined below. The NIH panel's guidance recommends prioritizing treatment uses of mAbs over all PEP. This MDH framework prioritizes PEP for highly immunocompromised individuals (as specified on Page 9) along with treatment uses, over PEP for immunocompetentindividuals, for two reasons. First, highly immunocompromised individuals face extremely high risk of progression to severe COVID-19. Second, unlike immunocompetent individuals, immunocompromised patients who develop COVID-19 infection may progress to severe disease too quickly to reasonably allow them to access mAbs for treatment. Thus, to adequately protect this population, PEP for immunocompromised individuals should be managed differently than PEP for immunocompetent individuals. In addition, the NIH panel's guidance recommends prioritizing "unvaccinated or incompletely vaccinated individuals" over vaccinated ones in allocation of mAbs (as well as prioritizing vaccinated individuals who are immunocompromised). In allocating mAbs for treatment of COVID-positive patients, this MDH framework deviates from that guidance by permitting the prioritization of both vaccinated and unvaccinated individuals who are at very high risk of progression to severe COVID-19, even if they are not immunocompromised.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

This document provides ethical guidance regarding the allocation of mAbs. When the first mAb – bamlanivimab – was first made available through an EUA, it was anticipated that supply would be insufficient to meet need. The Minnesota Department of Health (MDH) and the Minnesota COVID-19 Ethics Collaborative (MCEC) developed Interim Ethical Guidance for Monoclonal Antibody Administration. That and subsequent versions of this guidance document are now superseded by this framework.

This document was developed by MDH working with a subgroup of the MCEC, including the co-leads, with additional clinical input, and was subsequently reviewed by MCEC. The document addresses relevant past guidance developed at MDH, key ethical values, and how allocation should occur both under conditions of scarcity and conditions of sufficient supply regarding: (1) allocation to hospitals and health systems throughout the state and (2) allocation among patients within each infusion or injection facility (which will initially be affiliated with hospitals).

MCEC recommends this ethical guidance be operationalized using a centralized system called the Minnesota Resource Access Platform (MNRAP). This centralized approach promotes consistency among institutions and systems across the state of Minnesota, which is ethically important because it:

- Enhances transparency and the trustworthiness of pandemic response throughout the state;
- Fosters a common standard of care and access, and so helps to ensure fairness; and
- Promotes equity in allocation for all Minnesotans, whether or not they are affiliated with a health system.

After adopting this framework in February 2021, and after requests from a small number of health care systems, MDH decided to permit some health systems to opt out of using MNRAP to allocate mAbs on the condition that these systems demonstrate that their allocation process meets the ethical requirements of this framework and is at least as fair and equitable as MNRAP. These conditions require that opted-out systems accept unaffiliated patients without disadvantaging them, and that they implement their own lottery process when their system is in scarcity, as defined either by insufficient doses or appointment slots to meet demand. The weighted lottery process should account for the same clinical and nonclinical factors as outlined in this guidance (refer to "Escalating approaches to scarce resource allocation" below for those specific requirements). Opted-out systems should also meet additional reporting requirements set by MDH to demonstrate their respective systems are performing as intended. Given the current state of mAb supply, there is the possibility that mAbs may need to be rationed due to scarcity. Thus, all systems that have not opted out of MNRAP should use MNRAP for all mAbs allocation decisions, and not supplement MNRAP with allocation processes internal to their respective systems. In other words, all patients for facilities that have not opted out of MNRAP should be run through the MNRAP system.

- 1087) 2021-12-27 The National Law Review: Will answers come in 2022? Supreme Court sets January 7 hearing on COVID Vaccine Mandates.

 https://www.natlawreview.com/article/will-answers-come-2022-supreme-court-sets-january-7-hearing-covid-vaccine-mandates
- **1088)** 2021-12-27 CDC: CDC updates and shortens recommended isolation and quarantine period for general population. https://www.cdc.gov/media/releases/2021/s1227-isolation-quarantine-guidance.html
- 1089) 2021-12-28 Villapando N, Villalpando R: Texas runs out of monoclonal antibody treatment to fight omicron variant of COVID-19. USA TODAY https://www.usatoday.com/story/news/nation/2021/12/28/texas-runs-out-monoclonal-antibody-sotrovimab-treatment-fight-omicron-covid/9031897002/

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

- 1090) 2021-12-28 Jacqueline A. O'Shaughnessy, Ph.D., Acting Chief Scientist, FDA, U.S. Food & Drug: Letter to Dawn O'Connell, Assistant Secretary for Preparedness and Response, Office of Assistant Secretary for Preparedness and Response, Office of the Secretary, U.S. Department of Health and Human Services: Most recent EUA Letter regarding COVID-19 Convalescent Plasma, December 28, 2021. https://www.fda.gov/media/141477/download
- 1091) 2021-12-29 Dorman JL: Former Surgeon General Jerome Adams says CDC officials wouldn't follow the new guidance 'for their own family.' INSIDER https://www.businessinsider.com/jerome-adams-criticizes-cdc-guidance-isolation-covid-19antigen-tests-2021-12
- 1092) 2021-12-30 NIH COVID-19 Treatment Guidelines: The COVIDF-19 treatment guidelines panel's statement on therapies for high-risk, nonhospitalized patients with mild to moderated COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-highrisk-nonhospitalized-patients/
- 1093) 2021-12-30 McCammon S, Doucleff M: Omicron causes record-breaking COVID cases in the U.S. and globally. NPR 2021 Dec. 30 https://www.npr.org/2021/12/30/1069027394/omicron-causes-record-breaking-covid-casesin-the-u-s-and-globally
- **1094)** 2021-12-30 Quintana A: Florida surgeon general unhappy with fed's distribution of monoclonal antibody treatments. WTSP 10 Tampa Bay https://www.wtsp.com/article/news/regional/florida/florida-surgeon-general-monoclonalantibody-treatment/67-0ad20411-2b32-41ad-bcb2-15d07c5cfc7c
- 1095) 2021-12-31 FDA: FDA authorizes first two oral antivirals for treatment of COVID-19 EUA for COVID-19 treatments and tests https://content.govdelivery.com/accounts/USFDA/bulletins/30221ce
- 1096) 2022-01-03 Anthes E: How accurate are at-home Covid test? Here's a quick guide. The New York Times. https://web.archive.org/web/20220210163820/https://www.nytimes.com/article/at-homecovid-tests-accuracy.html
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6795&ctitle=COVID-19%20CDC%20Info%20-

%20Disease%20Outbreak%20Information%20-

%20MUW&wn=micrositeCollectionViewerMed&wf=/TemplatePackage/contrib/widgets/mi crositeCollectionViewerMed/&wid=micrositeCollectionViewerMed1&mMode=widget&mP age=&mChannel=&cdcCollectionid=403305&cdcTheme=theme1&cdcGeotag=%7B%27con tinent%27:%20%276255149%27,%20%27country%27:%20%276252001%27,%20%27state %27:%20%274436296%27,%20%27region%27:%20%274434357%27%20%7D&cdcDataid =404908&chashOptMode=out#!/detail/413605

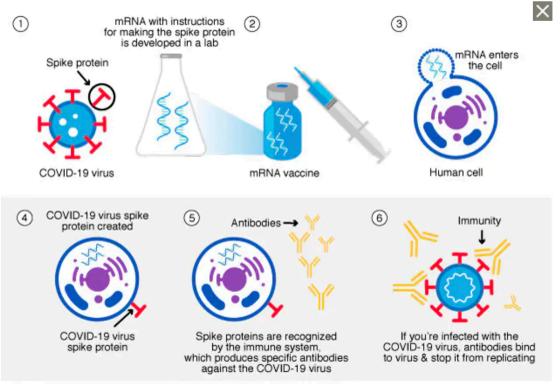
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Among 1,228,664 persons who completed primary vaccination during December 2020–October 2021, severe COVID-19-associated outcomes (0.015%) or death (0.0033%) were rare. Risk factors for severe outcomes included age ≥65 years, immunosuppressed, and six other underlying conditions. All persons with severe outcomes had at least one risk factor; 78% of persons who died had at least four.

- 1102) 2022-01-11 American Red Cross: Red Cross declares first-ever blood crisis amid omicron surge. https://www.redcross.org/about-us/news-and-events/pressrelease/2022/blood-donors-needed-now-as-omicron-intensifies.html
- 1103) 2022-01-12 Minnesota Department of Health: Ethical framework for allocation of Monoclonal Antibodies during the COVID-19 Pandemic. https://www.health.state.mn.us/diseases/coronavirus/hcp/mabethical.pdf
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- 1105) 2022-01-18 Mayo Clinic Staff: Different types of COVID-19 vaccines: How they work. https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-ofcovid-19-vaccines/art-20506465;

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mRNA vaccine cartoon:



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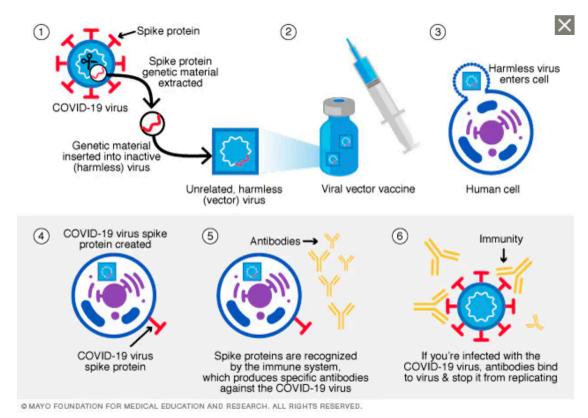
mRNA vaccine

A mRNA vaccine is made using mRNA that gives your cells instructions for how to make the spike protein found on the surface of the COVID-19 virus. After vaccination, your immune cells begin making the spike protein and displaying them on cell surfaces. This causes your body to create antibodies that can fight the COVID-19 virus.

https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-ofcovid-19-vaccines/art-20506465#dialogId29607008;

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Viral vector vaccine



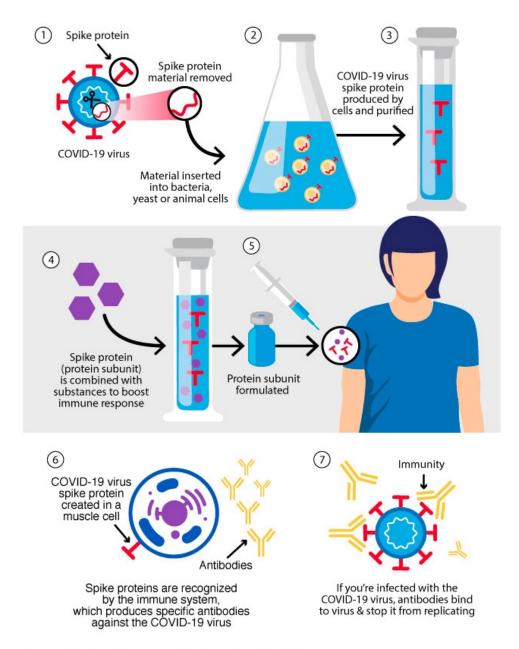
Viral vector vaccine

A viral vector vaccine is made when genetic material from a COVID-19 virus is inserted into a unrelated, harmless virus. When the viral vector gets into your cells, it delivers genetic material from the COVID-19 virus that gives your cells instructions for how to make the spike protein found on the surface of the COVID-19 virus. Once your cells displace the spike proteins on their surfaces, your immune system creates antibodies that can fight the COVID-19

https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-ofcovid-19-vaccines/art-20506465#dialogId17927109 :

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Protein subunit vaccine:



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Protein subunit vaccine

Subunit vaccines include only the parts of a virus that best stimulate your immune system. This type of COVID-19 vaccine contains harmless S proteins. Once your immune system recognizes the S proteins, it creates antibodies and defensive white blood cells. If you later become infected with the COVID-19 virus, the antibodies will fight the virus

https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465#dialogId5857171

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- 1106) 2022-01-18 Exact Sciences Corp: Exact sciences presents data showing improved accuracy of second-generation Cologuard test and progress toward and progress toward an even better colorectal cancer screening solution for patients.
 https://investor.exactsciences.com/investor-relations/press-releases/press-release-details/2022/Exact-Sciences-Presents-Data-Showing-Improved-Accuracy-of-Second-generation-Cologuard-Test-and-Progress-Toward-an-Even-Better-Colorectal-Cancer-Screening-Solution-for-Patients/default.aspx
- 1107) 2022-01-19 NIH COVID-19 Treatment Guidelines: The COVID-19 Treatment Guidelines Panel's Statement on therapies for high-risk, nonhospitalized patients with mild to moderate COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/
- 1108) 2022-01-21 O'Shaughnessy JA: FDA letter to Gilead Sciences, Inc. ...On January 21, 2022, FDA approved a supplemental application to NDA 214787 for Veklury expanding the approved uses to include the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg), with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. ...now authorizing Veklury for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of are weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are hospitalized, or are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. https://www.fda.gov/media/137564/download
- 1109) 2022-01-21 FDA: FDA takes actions to expand use of treatment for outpatients with mild-to-moderate COVID-19. https://www.fda.gov/news-events/press-announcements/fda-takes-actions-expand-use-treatment-outpatients-mild-moderate-covid-19
- 1110) 2022-01-24 Regeneron: U.S. Food and Drug Administration revises Emergency Use Authorization for REGEN-COV® (casirivimab and imdevimab) antibody cocktail due to Omicron Variant. https://investor.regeneron.com/static-files/cf13b06f-b874-4910-b583-c3c93c67a8f8
- 1111) 2022-01-24 O'Shaughnessy JA: EUA 094 letter to Eli Lilly and Company to limit the use of Eli Lilly's monoclonal antibody cocktail due to resistance of omicron variant. https://www.fda.gov/media/145801/download ...On January 24, 2022, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the December 22, 2021 letter in its entirety, to further limit the use of bamlanivimab and estesevimab administered together for treatment of COVID-19 or as post-exposure prophylaxis of COVID-19 to exclude geographic regions

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where, based on available information including variant susceptibility to these drugs and regional variant frequency, infection, or exposure is likely due to a variant that is nonsusceptible to bamlanivimab and etesvimab. Corresponding revisions have also been made to the authorized Fact Sheets.

- 1112) 2022-01-24 Murphy J: Fauci expects most states to reach peak omicron by February. Close to half already have. NBC News—The Data Point https://www.nbcnews.com/news/all/fauci-omicron-surge-february-2022-states-n1287935
- 1113) 2022-01-24 U.S. Food & Drug: Coronavirus (COVID-19 update: FDA limits use of certain monoclonal antibodies to treat COVID-19 Due to the Omicron variant. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fdalimits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron
- **1114)** 2022-01-24 Alu A, Chen L, Lei H, Wei Y, Tian X, Wei X: Intranasal COVID-19 vaccines: From bench to bed. The Lancet 2022 Feb 1; 76, 103841. https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(22)00025-1/fulltext
- 1115) 2022-01-25 Blake A: DeSantis, conservatives erupt over FDA pulling monoclonal antibodies shown to be ineffective against omicron. The Washington Post. https://www.washingtonpost.com/politics/2022/01/25/conservatives-led-by-desantis-eruptover-another-unproven-coronavirus-treatment/

...The Food and Drug Administration announced Monday that it would halt emergency-use authorizations for two monoclonal antibody therapies, one made by Regeneron Pharmaceuticals and one by Eli Lilly. At least with these monoclonal antibodies, unlike hydroxychloroquine and ivermectin, there was evidence they were once quite effective; that's just not the situation we find ourselves in at this point.

The FDA decision has led to a vehement outcry from some on the right, including the Republican who has most forcefully promoted monoclonal antibodies: Florida Gov. Ron DeSantis.

DeSantis said Monday that President Biden "has forced medical pros to choose treating their patients or breaking the law."

The governor added Tuesday moring, "Without a shred of clinical data to support its decision, the Biden Administration has revoked the emergency use authorization for lifesaving monoclonal antibody treatments."

DeSantis's criticism has been cheered and echoed by many on the right, including Fox News's Sean Hannity.

Going quite a bit further, DeSantis spokeswoman Christina Pushaw on Monday night even pointed a claim by a conservative conspiracy theorist that "the FDA is trying to make it so that people in Florida die of Covid. They'll kill people to harm Republicans." By Tuesday morning, she promoted another baseless claim that the decision was made "so Fauci-Pfizer can get a few extra points in the stock market."

----- May 30, 2022 -----

...As Nature reported more than a month ago, preliminary studies suggested that monoclonal antibody therapies, including the ones the FDA has not halted, showed virtually no efficacy against the omicron variant. https://www.nature.com/articles/d41586-021-03829-0

Here are some excerpts from one of the studies, which cites the Regeneron therapy (casirivimab and imdevimab) and the Eli Lilly therapy (bamlanivimab and estesevimab):...

- 1116) 2022-01-25 U.S. Food and Drug Administration: Emergency Use Authorization. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
- 1117) 2022-01-25 Troxel AB, Petkova E, Goldfeld K, Liu M, Tarpey T, Wu Y, Wu D, Agarwal A, Avendano-Solá, Brainbridge E, Bar KJ, Devos T, Duarte RF, Gharbharan A, Hsue PY, Kumar G, Luetkemeyer AF, Mayfroidt G, Nicola AM, Mukherjee A, Ortigoza MB, Pirofski LA, Rijders BJA, Rokx C,Sancho-Lopez A, Shaw P, Tebas P, Yoon HA, Grudzen C, J Association of convalescent plasma treatment with clinical status in patients hospitalized with COVID-19, A meta-analysis. JAMA Network | Open. 2022 January 25: 5(1): e2147331: 1-15.
 https://web.archive.org/web/20220203022011/https://jamanetwork.com/journals/jamanetwor
- 1118) 2022-01-25 Tin A: How can I get Paxlovid, the COVID-19 pill? Access to COVID treatments remains a challenge. CBS News. https://www.cbsnews.com/news/covid-19-paxlovid-pill-monoclonal-antibodies-treatments/

kopen/fullarticle/2788377

- **1119)** 2022-01-27 FDA: Know your treatment options for COVID-19. https://www.fda.gov/consumers/consumer-updates/know-your-treatment-options-covid-19
- 1120) 2022-01-27 Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, Oguchi G, Ryan P, Nielsen BU, Brown M, Hidalgo A, Sachdeva Y, Mittal S, Osiyemi O, Skarbinski J, Juneja K, Hyland RH, Osinusi A, Chen S, Camus G, Abdelghany M, davies S, Behennarenton N, Duff F, Marty FM, Katz MJ, Ginde AA, Brown SM, Schiffer JT, a d Hill JA for the GS-US-540-9012 (PINETREE) Investigators. Early Remdesivir to prevent progression to severe Covid-19 in outpatients. New Engl J Med 2022 Jan 27; 386 (4): 305-315. https://www.nejm.org/doi/full/10.1056/NEJMoa2116846 with Supplementary Appendix https://www.nejm.org/doi/suppl/10.1056/NEJMoa2116846/suppl_file/nejmoa2116846_appendix.pdf
- 1121) 2022-02 Paneth N, Casadevall A, Pirofski L, Henderson JP, Grossman BJ, Shoham S, Joyner MJ: WHO covid-19 drugs guideline: reconsider using convalescent plasma. BMJ 2022 February; 376: o295. https://www.bmj.com/content/376/bmj.o295
- 1122) 2022-02 Alu A, Chen L, Yuquan HL, Tian WX, Wei X: Intranasal COVID-19 vaccines: From bench to bed. www.thelancet.com 2022 Feb; 76: 1-16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8785603/pdf/main.pdf

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- 1123) 2022-02-01 NIH: COVID-19 Treatment Guidelines: Anti-SARS-CoV-2 Monoclonal Antibodies. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2antibody-products/anti-sars-cov-2-monoclonal-antibodies/
- 1124) 2022-02-03 IDSA Guideline on the Treatment and Management of COVID-19: Convalescent Plasma. https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt---convalescent-plasma-2022-02-03.pdf
- 1125) 2022-02-06 Gastroenterology consultants of San Antonio: The truth about Cologuard tests. https://www.gastroconsa.com/the-truth-about-cologuard-tests/
- 1126) 2022-02-11 O'Shaughnessy JA: FDA EUA letter to Eli Lilly and Company: Bebtelovimab is a neutralizing IgG1 monoclonal antibody that binds to an epitope within the receptor binding domain of the spike protein of SARS-CoV-2. Betelovimab is not FDA approved for any uses, including use as treatment for COVID-19. https://www.fda.gov/media/156151/download
- 1127) 2022-02-11 FDA News Release: Coronavirus (COVID-19) update: FDA authorizes new monoclonal antibody for treatment of COVID-19 that retains activity against omicron variant. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19retains#:~:text=The%20FDA%20is%20carefully%20monitoring,2%20omicron%20subvaria nt.
- 1128) 2022-02-14 Forman R: COVID Booster goes to the nasal cavity, where it will be most effective—Iwasaki A. Yale School of Medicine. https://medicine.yale.edu/newsarticle/nasal-approach-to-covid-vaccination-gains-traction-at-vale/
- 1129) 2022-02-15 Herscher M: Nearly half of state mask mandates have ended in the past 3 weeks. NBC News -The Data Point. https://www.nbcnews.com/news/us-news/maskmandate-map-february-2022-n1289093
- 1130) Ducharme J: Nasal vaccines could help stop COVID-19 from spreading If scientists can get them right. TIME. https://time.com/6148257/nasal-vaccines-covid-19/
- 1131) 2022-02-16. Andrus CH: Thank you letter to Gilead Sciences for providing the reference regarding the date of completion of Phase 1 remdesivir trial.

From: Charles.Andrus@va.gov, To: Public affairs@gilead.com,

Cc: Charles.Andrus@va.gov, candrus600@aol.com, Anthony.Fauci@nih.hhs.gov, kara.harris@nih.hhs.gov, Janet.Woodcock@fda.hhs.gov, Denise.Hinton@hhs.gov, Jacqueline.OShaughnessy@fda.hhs.gov, michael.hogan@va.gov,

Subject: RE: Phase 1 remdesivir trial result

Date: Wed, Feb 16, 2022 3:25 pm

Attachments: 3 Andrus SLU cv 8_11_2021.docx (7964K), ----- May 30, 2022 -----

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Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

2/16/2022

NIAID Case #12276

Dear Gilead:

Thank you for forwarding this article to me: Humeniuk R, Mathias A, Huyen C, Osinusi A, Shen G, Chng E, Ling J, Wu A, German P: Safety, Tolerability, and Tolerability, and Pharmacokinetic of Remdesivir, An antiviral for Treatment of COVID-19, in Healthy Subjects. Clin Transl Sci 2020; 13, 896-906: Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID 19, in Healthy Subjects (wiley.com). I have attached a copy of my CV so you know who I am. Over my decades of involvement with the Veterans Health Administration (VHA), U.S. Department of Veterans, I have attempted to be an advocate for each and every individual Veteran patient that presented to me. My biggest challenge was to have the phrase in VHA Handbook 1400.1 on Resident Supervision revised (after ~50 years): Level 3: Attending Surgeon not present, immediately available. What was condoned by the inappropriate application of Level 3 was that on nights, weekends, holidays, family get togethers, etc., some University Attending Surgeons would staff residents in the OR from afar (ghost surgery). Twenty years ago, I fought for that change all the way to the U.S. Court of Appeals for the Federal Circuit in Andrus v VA, Case 03-3162—in which the court per curium "failed to rule." I lost all my battles with the VA; but, in the end, all Attending Surgeons-of-Record in the VA today are required to be present in the OR suite during every individual Veterans' operation which is definitely to the betterment of every Veteran patient. The VA saved face by: 1.) changing VAH Handbook from 1400.1 to VAH Handbook 1400.01 so you can't find previous versions electronically if you don't know the previous URL.; 2.) as is common practice today, in the agencies of the Executive Branch of the Federal Government, electronically overwrite documents without designating what has been rescinded or that there was even a previous document; and 3.) I became and still am an unperson in the VA from 4/1982-8/2016 since my Official Personnel File (OPF) has been misplaced/lost. Thus, from April 1982 to August 2016, I don't exist in the VA until I returned in August 2016, as an Attending Physician and General Surgeon at the St. Louis VAMC. My VA service from 1982 to 2002 does not exist "officially" even though from 8/1996 to 1/2002, I was the Chief of Surgery, Edward Hines, Jr. VAH (the first hospital of the University-VA affiliation in 1946 under PL-79-293); and I was interviewed for the position of Under Secretary for Health

(USH) of the Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (DVA) on the 10th floor of VACO (across Lafyette Square from *The White House*) on the afternoon of December 10, 1999. I am telling you this, so I can put in context for you the convoluted process regarding Remdesivir that parallels that which occurred to me in my fight to stop Physically Unsupervised resident surgeons by VA misdirection and obfuscation twenty years ago. Today, by changing URLs, electronic overwriting, and semantics, the FDA, the NIH, the CDC, the VA, etc. have somewhat stretched the truth before the American people.

I thank you for forwarding the reference regarding the Phase I studies completed for Remdesivir (RDV). As is quoted in the article:

----- May 30, 2022 -----

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On May 1, 2020, based on available data from to global clinical trials, the US Food and Drug Administration (FDA) granted emergency use authorization to allow RDV to treat adults and children hospitalized with severe COVID-

19^{19,22,23} Based on these clinical data, RDV has been approved for the treatment of adults and pediatric patients in

Japan.²⁴ This paper describes the safety and pharmacokinetics (PKs) of the solution and lyophilized formulations of i.v. RDV administered to healthy participants in the two first-in-human (FIH) phase I studies.

The above paragraph suggests that the FDA issued the EUA after review of the two first-in-human phase I studies involving Remdesivir (VEKLURY) and that review occurred at least by May 1, 2020, which means that phase I human trials were deemed safe and implies that the phase I trials *de facto* were completed—BUT, that presented multiple ethical and legal dilemmas for the FDA, the NIH, etc.

- 1. The FDA issued the first Remdesivir EUA on May 1, 2020 (which was the date when Dr. Fauci announced Remdesivir from the Oval Office); yet by making it an EUA, Remdesivir,-- the FDA was defining Remdesivir as an "unapproved" drug in the treatment of COVID-19
- 2. As phase II/III clinical trials proceeded, prospective participants who had contracted COVID-19 should have been made aware in their Informed Consent that with The Right to Try Act, PL-115-176 that they could still be afforded Remdesivir by non-participation in the mandated RCT placebo trials—for that matter, all of America should have been told of this by the FDA! As the Phase I studies *de facto* were completed, any American could have asked for Remdesivir under PL-115-176 and should have received it!
- 3. As I am sure that you are well-aware that Remdesivir is "a single diastereomeric monophoramidate prodrug that inhibits viral RNA polymerases" which works best during the initial viremic phase of COVID-19—rather than in the later severe disease phases of cytokine cascade and bradykinin storm. Unfortunately, with the issuance of the EUA on May 1, 2020, "the US Food and Drug Administration (FDA) granted emergency use authorization to allow RDV to treat adults and children hospitalized with severe COVID-19^{19,22,23}." In fact, the FDA removed the severity stipulation quietly--not notifying the American public of this significant retraction--on August 28, 2020. In the FDA January 21, 2022 letter to Madelyn Low, MBS, Manager, Regulatory Affairs, Gilead Sciences, Inc., https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fda-authorization-letter.pdf?

 la=en&hash=FD3737583BE0E4DF710ADB36AEAA2DBD, there are 8 references on pages 1 and 2 in which the Acting Chief Scientist of FDA outlined the chronology regarding Remdesivir including the August 28, 2020 retraction of the soverity of illness stipulation: "FDA revised

and 2 in which the Acting Chief Scientist of FDA outlined the chronology regarding Remdesivir including the August 28, 2020 retraction of the severity of illness stipulation: "...FDA revised authorized use of Veklury to no longer limit its use for the treatment of patients with severe disease." (How could Remdesivir being an "unapproved" drug in the treatment of COVID-19 under the FDA's EUAs standards become a drug that the FDA was officially revising authorization so it could be given early in the course of the disease? It seems like a bunch of semantics; but if that bunch of semantics limits the rights of individuals in America, that is wrong.

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- 4. "On October 22, 2020, FDA also approved NDA 214787 for Veklury for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 Kg) requiring hospitalization." At this point, Remdesivir (VEKLURY) was designated by the FDA as a prescription drug (NDA 214787) on October 22, 2020.
- 5. In November 2020, the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs issued for the fully-FDA- authorized-prescription drug, VEKLURY, NDA 214787 the: "Remdesivir (VEKLURY) Criteria for Use" of how to administer Remdesivir with the severity Inclusion Criteria exclusively included that had been removed previously on August 28, 2020 by the FDA:

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dyn and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making

SUIDAN SXCLUSI	fordize and improve the quality of potient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS ICE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE ION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF COMMITTEE AND PHARMACY SERVICES.
The Pro	duct Information should be consulted for detailed prescribing information.
ee the	VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.
Exc	lusion Criteria
f the a	nswer to ANY item below is met, then the patient should NOT receive remdesivir
_ 1	Treated for COVID-19 as an outpatient
_ /	AST or ALT > 5 times the upper limit of normal
_ '	Hospitalized patients but NOT requiring supplemental oxygen*
	Concomitant use of hydroxychloroquine or chloroquine
_ (Current eGFR < 30 mL/min **
ncl	usion Criteria
The fol	lowing must be fulfilled in order to meet criteria for remdesivir
	Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
Sup	plemental Information
Recom or who	emended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration apy has not been given
Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis	
*Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks, especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance.	
	ndesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with teroids in patients who have recently been intubated, occording to the NIH Treatment Guidelines for COVID-19
	ed: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program

Updated version may be found at PBM INTERnet or PBM INTRAnet

6. When I had a patient denied Remdesivir by the Infectious Diseases service quoting the November VA directive, I contacted Richard Stone, M.D., VHA Chief Medical Executive (the Trump Administration's title for the Under Secretary for Health, VHA, DVA). Dr. Stone contacted VA Pharmacy Management Services and the Medical Advisory Board. At first, the VA responded

----- May 30, 2022 -----

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

to me. But when the VA became evasive, I contacted the FDA, the NIAID (Case #12276), and wrote a letter to the editors of the The New England Journal of Medicine. None responded to me.

7. I recently had a patient admitted to the Surgical Service who had newly turned COVID-19 positive (less than 24 hours from negative to positive). The recommendations from the same Infectious Diseases service was that if the patient had any symptomatology like headache or neck pain, give three days of Remdesivir; and if the patient develops a cough, give five days of Remdesivir and dexamethasone. By the time of that consult, the CDC had stated a month before that Regeneron's and Eli Lilly's monoclonal cocktails were ineffective against COVID-19, omicron variant; and, thus, GlaxoSmithKline's sotrovimab was and is being de facto rationed at present time.

Once again, I thank all involved in addressing my question at Gilead regarding if a phase I study had been completed in the case of Remdesivir. You were all very professional and willing to listen - and, most of all, my personal thanks as a Federal Physician and Surgeon for you have provided this information which may become an outstanding service for the people of the United States of America.

Thank you,

Charles Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine

Chief and Attending General Surgeon, Unit II (SLU) General Surgery division, Surgical Service, John Cochran (112JC), St. Louis, MO 63106

Office phone: 314-652-4100 ext 54463 Beeper: 314-491-2417

Home phone: 314-455-9482

P.S. I hope this e-mail will initiate an overall discussion regarding transparency by the agencies of the U.S. Government in regards to the EARLY (< 72 hours from diagnosis) administration with intent of synergism of COVID-19 Convalescent Plasma, COVID-19 monoclonal antibodies, Remdesivir and other future antivirals, etc. Respectfully, Charles H. Andrus, M.D., F.A.C.S.

From: Public Affairs < Public affairs@gilead.com> Sent: Wednesday, February 16, 2022 7:54 AM

To: Andrus, Charles H. (STL) < Charles. Andrus@va.gov> **Subject:** [EXTERNAL] Phase 1 remdesivir trial results

Dr. Andrus,

You can find the published results of the Phase 1 remdesivir trial here: https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.12840 (reference #466 of this chronological bibliography)

Thank you for your inquiry,

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

Gilead Public Affairs

- 1132) 2022-02-22 Adler B: Trump praises Putin's 'genius' incursion into Ukraine. https://news.yahoo.com/trump-praises-putins-genius-incursion-into-ukraine-234001858.html
- 1133) 2022-02-25 CDC: COVID-19—People with certain medical conditions.

 https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
- 1134) 2022-02-27 Campbell C: 'Almost treasonous': Romney condemns GOP backing Putin. https://www.aol.com/news/almost-treasonous-romney-condemns-gop-171557057.html
- 1135) 2020-02-27 Moore M: US hints at war-crimes tribunal after Ukraine accuses Russia of genocide. New York Post. https://nypost.com/2022/02/27/us-hints-at-war-crimes-tribunal-after-ukraine-accuses-russia-of-genocide/
- 1136) 2022-02-27 Reuters: World Court: Ukraine has filed suit against Russia, citing false genocide claims. https://www.reuters.com/world/europe/icc-says-may-investigate-possible-war-crimes-after-russian-invasion-ukraine-2022-02-25/
- 1137) 2022-02-27 Bancroft H, Gregory A, Rai A: Ukraine-Russian news live: Putin puts nuclear forces on high alert as Zelensky calls for foreign fighters. Independent. https://www.independent.co.uk/news/world/europe/russia-ukraine-crisis-latest-putin-kyiv-zelensky-war-update-b2024247.html
- 1138) 2022-02-28 iSpot.tv: Pfizer, Inc. TV Spot, 'Move Fast: Oral Treatment. https://www.ispot.tv/ad/bAea/pfizer-inc-move-fast-oral-treatment

DEAR MR. PRESIDENT:

WHAT FOLLOWS IS THE FDA DISCLAIMER REGARDING THE ADVERTIZEMENT IN WHICH THE "ORAL MEDICATION in the treatment of COVID-19" IS AUTHORIZED UNDER AN EUA BUT \overline{NOT} Approved by the FDA FOR THE USE TO TREAT EARLY (<120 HOURS FROM ONSET) COVID 19.

Mr. President: You may ask, Why the legal semantics? Well, it is probably a violation of Federal Law that Pfizer is advertising Paxlovid (the advertisement never calls the antiviral by name—as Merck also has an experimental oral antiviral authorized by the FDA under an

EUA and both are under EUAs); **While** Remdesivir (VEKLURY) **HAS BEEN AN FDA approved and authorized PRESCRIPTION intravenous antiviral DRUG**

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designated FOR use in THE EARLY TREATMENT OF COVID-19 SINCE October 22, 2020. In short, your administration has bought 20 million boxes (30 pills per box (1 five day treatment dose) for a total of 600 million—0.6 billion pills—of an experimental antiviral, PAXLOVID, in the "TEST to TREAT initiative"—which is outstanding. These experimental oral antivirals under EUAs are in direct commercial competition with an FDA approved, authorized intravenous prescription drug: VEKLURY (Remdesivir) which could have been administered in EVERY INFUSION CENTER, OUTPATIENT SURGICENTER, AND HOSPITAL IN THE U.S.A. FOR THE LAST 20 MONTHS—but was withheld by general medical ignorance, the pharmaceutical industry's arrogance and greed, and federal incompetence and conflicts-of-interests.

Charles H. Andrus, M.D., F.A.C.S., May 15, 2022

https://www.covid19oralrx-

patient.com/?source=google&HBX PK=s paxlovid&skwid=43700068270576697&gclid=E AIaIQobChMIsIiA49fY9gIVk5JbCh0sxA4PEAAYASAAEgLZs D BwE&gclsrc=aw.ds

Authorized Use

The FDA has authorized the emergency use of PAXLOVID, an investigational medicine, for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with a positive test for the virus that causes COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death, under an EUA.

PAXLOVID is investigational because it is still being studied. There is limited information about the safety and effectiveness of using PAXLOVID to treat people with mild-to-moderate COVID-19.

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Pfizer

PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets)

Now Authorized for Emergency Use

PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

1139) 2022-03-01 Biden J: Remarks of President Joe Biden – State of the Union Address as Prepared for Delivery. *The White House, Briefing Room, March 1, 2022, Speeches and Remarks.* https://www.whitehouse.gov/briefing-room/speeches-remarks/2022/03/01/remarks-of-president-joe-biden-state-of-the-union-address-as-delivered/

...I remember when my Dad had to leave our home in Scranton, Pennsylvania to find work. I grew up in a family where if the price of food went up, you felt it.

That's why one of the first things I did as President was fight to pass the American Rescue Plan.

Because people were hurting. We needed to act, and we did.

Few pieces of legislation have done more in a critical moment in our history to lift us out of crisis.

It fueled our efforts to vaccinate the nation and combat COVID-19. It delivered immediate economic relief for tens of millions of Americans.

Helped put food on their table, keep a roof over their heads, and cut the cost of health insurance.

And as my Dad used to say, it gave people a little breathing room.

And unlike the \$2 Trillion tax cut passed in the previous administration that benefitted the top 1% of Americans, the American Rescue Plan helped working people—and left no one behind. ...

... For more than two years, COVID-19 has impacted every decision in our lives and the life of the nation.

And I know you're tired, frustrated, and exhausted.

But I also know this.

Because of the progress we've made, because of your resilience and the tools we have, tonight I can say

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

we are moving forward safely, back to more normal routines.

We've reached a new moment in the fight against COVID-19, with severe cases down to a level not seen since last July.

Just a few days ago, the Centers for Disease Control and Prevention—the CDC—issued new mask guidelines.

Under these new guidelines, most Americans in most of the country can now be mask free.

And based on the projections, more of the country will reach that point across the next couple of weeks.

Thanks to the progress we have made this past year, COVID-19 need no longer control our lives.

I know some are talking about "living with COVID-19". Tonight – I say that we will never just accept living with COVID-19.

We will continue to combat the virus as we do other diseases. And because this is a virus that mutates and spreads, we will stay on guard.

Here are four common sense steps as we move forward safely.

First, stay protected with vaccines and treatments. We know how incredibly effective vaccines are. If you're vaccinated and boosted you have the highest degree of protection.

We will never give up on vaccinating more Americans. Now, I know parents with kids under 5 are eager to see a vaccine authorized for their children.

The scientists are working hard to get that done and we'll be ready with plenty of vaccines when they do.

We're also ready with anti-viral treatments. If you get COVID-19, the Pfizer pill reduces your chances of ending up in the hospital by 90%.

We've ordered more of these pills than anyone in the world. And Pfizer is working overtime to get us 1 Million pills this month and more than double that next month.

And we're launching the "Test to Treat" initiative so people can get tested at a pharmacy, and if they're positive, receive antiviral pills on the spot at no cost.

If you're immunocompromised or have some other vulnerability, we have treatments and free high-quality masks.

We're leaving no one behind or ignoring anyone's needs as we move forward.

And on testing, we have made hundreds of millions of tests available for you to order for free.

Even if you already ordered free tests tonight, I am announcing that you can order more from covidtests.gov starting next week.

Second – we must prepare for new variants. Over the past year, we've gotten much better at detecting new variants.

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

If necessary, we'll be able to deploy new vaccines within 100 days instead of many more months or years.

And, if Congress provides the funds we need, we'll have new stockpiles of tests, masks, and pills ready if needed.

I cannot promise a new variant won't come. But I can promise you we'll do everything within our power to be ready if it does.

Third – we can end the shutdown of schools and businesses. We have the tools we need.

It's time for Americans to get back to work and fill our great downtowns again. People working from home can feel safe to begin to return to the office.

We're doing that here in the federal government. The vast majority of federal workers will once again work in person.

Our schools are open. Let's keep it that way. Our kids need to be in school.

And with 75% of adult Americans fully vaccinated and hospitalizations down by 77%, most Americans can remove their masks, return to work, stay in the classroom, and move forward safely.

We achieved this because we provided free vaccines, treatments, tests, and masks.

Of course, continuing this costs money.

I will soon send Congress a request.

The vast majority of Americans have used these tools and may want to again, so I expect Congress to pass it quickly.

Fourth, we will continue vaccinating the world.

We've sent 475 Million vaccine doses to 112 countries, more than any other nation.

And we won't stop.

We have lost so much to COVID-19. Time with one another. And worst of all, so much loss of

Let's use this moment to reset. Let's stop looking at COVID-19 as a partisan dividing line and see it for what it is: A God-awful disease.

Let's stop seeing each other as enemies, and start seeing each other for who we really are: Fellow Americans.

We can't change how divided we've been. But we can change how we move forward—on COVID-19 and other issues we must face together. ...

- May 30, 2022 ---

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...And fourth, let's end cancer as we know it.

This is personal to me and Jill, to Kamala, and to so many of you.

Cancer is the #2 cause of death in America—second only to heart disease.

Last month, I announced our plan to supercharge the Cancer Moonshot that President Obama asked me to lead six years ago.

Our goal is to cut the cancer death rate by at least 50% over the next 25 years, turn more cancers from death sentences into treatable diseases.

More support for patients and families.

To get there, I call on Congress to fund ARPA-H, the Advanced Research Projects Agency for Health.

It's based on DARPA—the Defense Department project that led to the Internet, GPS, and so much more.

ARPA-H will have a singular purpose—to drive breakthroughs in cancer, Alzheimer's, diabetes, and more.

- 1140) 2022-03-01 Satyanarayana M: Nasal spray COVID preventives are finally in development Different methods of drug delivery give us more tools to fight disease. Scientific American. https://www.scientificamerican.com/article/nasal-spray-covid-preventives-are-finally-in-development1/
- 1141) 2022-03-06 Brewster A, Gomez Fin: Trump renews NATO criticism after Russia's invasion of Ukraine, and also say "vote counter" can be more important than candidate. CBS News https://www.cbsnews.com/news/trump-russia-ukraine-nato-elections/

Trump's remarks came about 24 hours after <u>former Vice President Mike Pence took several shots</u> <u>at Trump</u> during his address to the same donor retreat, which is taking place in New Orleans.

Pence told them Friday evening that "there is no room in this party for apologists for Putin" — days after Trump had referred to the Russian president as "smart" and "savvy." On Saturday evening, Trump mentioned that "somebody called me a Putin apologist the other day," but didn't bring up Pence, according to a source.

- 1142) 2022-03-07 Casadevall A, Grossman BJ, Joyner MJ, Henderson JP, Paneth N, Pirofski LA, Shoham S: National COVID-19 Convalescent Plasma Project. Last digitized for International Archive, March 7, 2022. https://ccpp19.org/about/index.html
- 1143) 2022-03-08 HHS.gov: Fact Sheet: Biden administration launches nationwide Test-to-Treat initiative ensuring rapid 'On the Spot' access to lifesaving COVID treatments. https://www.hhs.gov/about/news/2022/03/08/fact-sheet-biden-administration-launches-

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nationwide-test-treat-initiative-ensuring-rapid-on-spot-access-lifesaving-covidtreatments.html

1144) 2022-03-09 Rubin R: Once viewed as a promising COVID-19 treatment, convalescent plasma falls out of favor. JAMA network

https://jamanetwork.com/journals/jama/fullarticle/2790074?guestAccess

In the pandemic's initial dark days, physicians and patients and their families were desperate for effective COVID-19 treatments. They didn't yet have monoclonal antibodies or antiviral pills to lessen the ravages of the disease, so many turned to a therapy more than a century old.

At the very least, they figured, convalescent plasma, donated by people who'd recovered from COVID-19, couldn't hurt, and the SARS-CoV-2 antibodies it was presumed to contain could enhance patients' defenses against COVID-19.

"There was a preconceived notion of efficacy," H. Clifford Lane, MD, deputy director for clinical research and special projects at the National Institute of Allergy and Infectious Diseases, said in a recent interview.

Three reports from Wuhan, China, published in 2020 in *JAMA*, the *Proceedings of the* National Academy of Sciences, and the Journal of Medical Virology, showed that patients' viral load decreased and their symptoms improved following infusions of convalescent plasma. But the studies involved only a total of 21 patients; the authors of all 3 articles noted that clinical trials were needed to confirm the findings.

Nevertheless, while trials were being planned, US hospitals began infusing patients with COVID-19 with convalescent plasma through the US Food and Drug Administration's (FDA's) Expanded Access Program (EAP). Approximately 94 000 people hospitalized with COVID-19 in the US had received convalescent plasma infusions by August 2020, when the FDA ended the EAP and authorized the golden liquid for emergency use.

A December 2021 analysis of EAP data in PLOS Medicine demonstrated convalescent plasma's safety in patients hospitalized with COVID-19—the incidence of serious adverse events was less than 1%. But because the study didn't include a control or comparator group, "the data should not be used to infer definitive treatment effects," the authors noted.

As other COVID-19 treatments became available, convalescent plasma's early promise didn't pan out in randomized clinical trials. "I don't think convalescent plasma is a firstline therapy at this point," Kevin Schulman, MD, a professor of medicine at the Stanford University School of Medicine who has studied the treatment, said in an interview.

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Officer of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health, Bethesda, Maryland

Panic Instead of Science?

Convalescent plasma wasn't associated with clinical benefit in a recent JAMA Network Open meta-analysis that pooled findings from 8 randomized clinical trials involving 2341 hospitalized patients breathing without the aid of mechanical ventilation, 1231 of whom received the treatment.

A UK trial published too recently to be considered for inclusion in the meta-analysis reached a similar conclusion. It randomized 11 558 hospitalized patients—5% of whom were receiving invasive mechanical ventilation upon randomization—to receive usual care plus convalescent plasma or only usual care. Researchers found that convalescent plasma did not improve survival or progression to ventilation.

In addition, a recently published multicenter placebo-controlled trial randomized 511 high-risk outpatients with COVID-19 who came to emergency departments within 7 days of symptom onset. The study found that convalescent plasma didn't prevent disease progression.

"We've moved on," said Schulman, a coauthor of the emergency department trial. "Convalescent plasma is a great thing to think about very early in a pandemic."

Instead of providing an untested treatment to tens of thousands of patients in the EAP, multiple, large clinical trials could have been conducted, Schulman said. But, he added, a "huge amount of desperation" early in the pandemic "turned into panic, not into science."

Large clinical trials, with 2500 patients apiece, could have answered questions that still remain, such as identifying the optimal dose and timing of convalescent plasma treatment and which patients are likely to benefit, Schulman said.

"You could easily argue we underdosed patients" in his trial, Schulman acknowledged. "Our trial was the best we could do at the time."

All in the Timing?

Arturo Casadevall, MD, PhD, a leader of the National COVID-19 Convalescent Plasma Project, isn't ready to abandon a treatment he's championed since penning a Wall Street Journal op-ed about it in February 2020.

"In the spring of 2020, I really thought that convalescent plasma was a safety raft to new therapies that would be available in the fall," Casadevall, chair of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health, said in a recent interview.

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Casadevall said he would have liked to conduct clinical trials with some of the patients enrolled in the EAP, but funding wasn't available. Instead, he took a different approach to try to assess convalescent plasma's efficacy: He tracked the number of convalescent plasma units that blood banking organizations dispensed to hospitals per admission and COVID-19 deaths in the fall of 2020. Casadevall and his collaborators found a strong inverse correlation between convalescent plasma use per COVID-19 hospital admission and deaths from the disease occurring 2 weeks after admission.

The problem with the randomized trials is that they didn't treat patients soon enough to make a difference, Casadevall said.

Only trials in which patients receive convalescent plasma early in their infection could be expected to show a treatment benefit, he explained. By the time patients require hospitalization for COVID-19, the horse is already out of the barn. At that point, Casadevall said, inflammation is the problem, so anti-SARS-CoV-2 antibodies wouldn't help slow disease progression. (Similarly, no anti-SARS-CoV-2 monoclonal antibody product has been authorized for patients with severe COVID-19.) The National COVID-19 Convalescent Plasma Project has posted critiques of Schulman's study, the UK trial, and other research on its website.

Casadevall coauthored a recent multicenter trial that randomized 1225 outpatients whose COVID-19 symptoms had begun within 8 days before enrollment. The study, which hasn't been peer-reviewed, found that early administration of high-titer SARS-CoV-2 convalescent plasma reduced hospitalizations over the next 28 days by 54% compared with control plasma from donors who had not had COVID-19.

"High titer convalescent plasma is an effective early outpatient COVID-19 treatment with advantages of low cost, wide availability, and rapid resilience to variant emergence from viral genetic drift in the face of a changing pandemic," Casadevall and his coauthors concluded.

Limiting Its Use

Despite Casadevall's favorable finding, recently updated guidelines from the World Health Organization (WHO), the FDA, and the Infectious Diseases Society of America (IDSA) recommend only limited use of convalescent plasma, if that.

On February 8, 2022, IDSA strongly recommended against using convalescent plasma in patients hospitalized with COVID-19. Among ambulatory patients with mild to moderate disease who are at high risk of progression to more serious symptoms and have no other treatment options, infusing high-titer COVID-19 convalescent plasma within 8 days of symptom onset is better than not infusing it, according to the guideline, which described this as a conditional recommendation with low certainty of evidence.

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The FDA's most recent revision of the Emergency Use Authorization (EUA) for COVID-19 convalescent plasma, published December 28, 2021, limits treatment with high-titer COVID-19 convalescent plasma to patients who have immunosuppressive disease or are receiving immunosuppressive treatment.

Randomized clinical trials and observational studies show that convalescent plasma is unlikely to be associated with clinical benefit in immunocompetent individuals with COVID-19, according to the FDA.

Interestingly, the WHO recommends against its use for patients who aren't severely ill, calling the evidence for that position "certain." Convalescent plasma should be used only within clinical trials for severe and critical patients with COVID-19, the WHO said in December 2021.

In a letter to the BMJ, Casadevall and coauthors urged the WHO to reconsider, saying that the organization "avoided digging below the surface to ask critical questions about treatment timing, study populations, and antibody titre" of the convalescent plasma in the trials it considered.

For now, demand for convalescent plasma is low because the clinical trial findings in hospitalized patients have persuaded many physicians that it won't benefit any patients, Casadevall said. On top of that, he said, "Medicine has gotten used to working with therapies that are very well-defined. Plasma is a therapy where physicians are uncomfortable because every unit is different. To many people, that just doesn't feel right."

Lane is among those people. "It's not a uniform product," he noted. Assays suggested by the FDA measure only antibodies to the spike protein of 1 variant, so it's difficult to know the true level and nature of antibodies in a unit of convalescent plasma, Lane said.

And it's virtually impossible to judge a unit of plasma by its donor, Lane said. "Typically, the sicker you are, the better your antibodies." Younger people also tend to generate more antibodies than older people, he added. However, "the immune response to SARS-CoV-2 is highly variable."

Other COVID-19 treatments are standardized, so physicians can know exactly what they're giving patients, Lane said. "If you have an at-risk ambulatory patient with symptoms, you can give them Paxlovid [nirmatrelvir and ritonavir, Pfizer's antiviral pill], you can give them remdesivir. You can reduce their risk of being hospitalized 80% to 85%, and you know what you've given."

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Treatment: Passive Immunization: COVID-19 Convalescent Plasma and Antibodies and Antivirals

----- May 30, 2022 -----

Prevention: Active Immunization: Vaccines

Published Online: March 9, 2022. doi:10.1001/jama.2022.3214

Conflict of Interest Disclosures: Dr Schulman reports receiving personal fees from Novartis and from Frazier Healthcare Partners. Dr Casadevall reports that he is involved in convalescent plasma clinical trials at Johns Hopkins and serves on the scientific board of SAB Biotherapeutics, an antibody company.

- 1145) 2022-03-10 Takashita E, Kinoshita N, Kawaoka Y, and Others: Efficacy of antibodies and antiviral drugs against Covid-19 omicron variants. N Eng J Med 2022 March 10; 386(10): 995-998. https://www.nejm.org/doi/pdf/10.1056/NEJMc2119407?articleTools=true
- 1146) 2022-03-10 Katella K: 12 things to know about Paxloid, the latest COVID-19 pill. Yale Medicine https://www.yalemedicine.org/news/12-things-to-know-paxlovid-covid-19
- 1147) 2022-03-11 Adams B: Pfizer's softly, softly, COVID marketing approach continues with new drug ad FIERCE Pharma. https://www.fiercepharma.com/marketing/pfizers-softly-softly-marketing-approach-continues-new-paxlovid-covid-drug-ad
- 1148) 2022-03-11 Ellis R: Scientists identify new COVID variant called 'Deltacron'. WebMD https://www.webmd.com/lung/news/20220311/new-covid-variant-deltacron#:~:text=March%2011%2C%202022%20%2D%2D%2D%20A,the%20World%20Health%20Organization%20says.
- **1149)** 2022-03-14 Federal Trade Commission (FTC): Truth in Advertising. https://www.ftc.gov/news-events/topics/truth-advertising
- 1150) 2022-03-16 National COVID-19 Convalescent Plasma Project: National COVID-19 Convalescent Plasma Project. News Critiques of Trials. Last digitized capture by the Internet Archive, March 16, 2022. https://ccpp19.org/news/index.html
- 1151) 2022-03-17 FDA: EUA 105 letter to Pfizer regarding PAXLOID [nirmatrelvir, a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, copackaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentration to levels anticipated to inhibit SARS-CoV-2 replication. PAXLOID is not approved for any use, including treatment of COVID-19.] https://www.fda.gov/media/155049/download
 - II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized PAXLOVID will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Pfizer will supply PAXLOVID to authorized distributor(s)⁴, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;
- PAXLOVID may only be used by healthcare providers to treat mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk⁵ for progression to severe COVID-19, including hospitalization or death;

Limitations on Authorized Use

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.6
- PAXLOVID is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.
- PAXLOVID may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which PAXLOVID belongs (i.e., anti-infectives).⁷
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Time: The Crucial *Independent Variable* of the COVID-19 Pandemic

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Professor, Department of Surgery, Saint Louis University School of Medicine
Chief, Unit II (SLU) Section, Division of General Surgery,
Surgical Service (112), John Cochran (St. Louis) VAMC

June 7, 2020

Abstract:

Introduction: While awaiting a COVID-19 vaccine, can a longitudinal review of the reported statistics of four countries: China, Italy, Spain, and the USA provide insight into a better practice scenario?

Methods: Reported new daily COVID-19 positive case and new daily death numbers from China, Italy, Spain, and the USA were obtained from two databases. Linear and logarithmic regression analyses of scatter plots were applied to the downward trending portion of the daily number of cases and deaths to calculate predicted end-points of no new positive cases and no new deaths. While the downward trending slopes of the data from China, Italy, and Spain predict initial resolution of the epidemics in each of these countries by the end of the summer 2020, the logarithmic regression analyses of the present trend in USA database predicts many years to resolution.

Discussion: What is the USA doing differently compared to these three countries? China and Italy are reported to have used a significant amount of convalescent plasma (plasma from patients recovered from COVID-19 infection without detectable virus) in the passive immunization of COVID-19 positive patients. Emphasizing the necessity of finding a cure (a vaccine), we, in the USA, have inadvertently diminished before the public perception of the century-held beneficial concept of passive immunization provision to any immune-naïve, COVID-19 infected individual. The U.S. Food and Drug Administration (FDA) is legally mandated to regulate every aspect of blood therapy in the USA regarding all blood components collected, tested, and dispensed (>28 million components annually). Instead of abiding by the present federally-directed standard-of-care regarding blood component therapy of making plasma available to every appropriately licensed physician for any patient requiring plasma products (e.g.: fresh frozen plasma and cryoprecipitate), the FDA through the published "Recommendations" has mandated physician research participation and *de facto* patient coercion in research participation by requiring physician applications for Emergency Investigational New Drug numbers (eIND) thus excluding COVID-19 individuals not offered convalescent plasma and, by default, de facto non-research study non-participation. The Mayo Clinic has established a website in collaboration with the FDA to help facilitate implementation of the FDA "Recommendations." As of June 1, 2020, through this website, there has been a reported accrual of 7,157 physicians, 2,396 sites (44% of acute care hospitals), 18,543 infusions of convalescent plasma (1.02% of the 1.8 million COVID-19 positive patients) and 24,513 patients enrolled in this research study. Thus, 5970 accrued patients did not receive convalescent plasma – (e.g. protocol exclusion parameters, improved without treatment, died before infusion, etc.)

Conclusions: By the FDA issuing recommendations linking the dispensing of (convalescent) plasma exclusively to mandatory physician participation in research studies by requiring an Experimental Investigational New Drug application (eIND, Form 3926 FDA), the FDA has inadvertently established a discriminatory methodology in the dispensing of plasma contingent on *de facto* coerced participation in research studies which deviates from the standard-of-care in provision of plasma (a non-experimental blood product) to all persons requiring plasma overriding present statutory FDA policy of equity for all persons requiring blood products. This present analysis demonstrates that this FDA-mandated research

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participation has possibly, inadvertently minimized the universal application of convalescent plasma in the early treatment of COVID-19 infected patients (including high-risk-of-exposure individuals who become COVID-19 infected, e.g.: first responders, medical personnel, medical-facility housekeepers, etc.); and *de facto* has dismissed the importance of passive immunization as a temporizing initial treatment during any viral epidemic in the eyes of the American people.

Introduction: During this Coronavirus Disease 2019 (COVID-19) pandemic, social distancing, PPE, and staying-in-place have become mandated practices and mantra to various degrees throughout the world. Individual, governmental, and societal implementation, endurance, and consistency to these mandates have been variable. The populous response in the United States of America (USA) at all levels are at best reflective of Elisabeth Kübler-Ross's four of the five stages of the terminally ill patient: denial and isolation, anger, bargaining, and depression. The Johns Hopkins Dashboard and other databases like *Our World in Data* COVID-19 dataset accrue, report, and publish the new cases and new deaths on a daily basis. While awaiting the *Magic Bullet* of a vaccine, can a longitudinal review of the reported statistics of four countries which are in different phases of initial containment and representative in variability of response and reported mortality outcomes: China, Italy, Spain, and the United States of America (USA), imply a better practice scenario?

Methods: Raw data of daily reported new cases from the Johns Hopkins dashboard³ and daily reported deaths from the *Our World in Data* COVID-19 dataset⁴ between January 1, 2020 and May 23-24, 2020 were accumulated, plotted, and trended by date longitudinally regarding four countries: China—the index country now with possible successful initial containment of the epidemic, Italy and Spain who represent countries with some of the highest ratios of mortalities to COVID-19 positive cases in Europe; and the USA for it's overwhelming magnitude of reported positive cases and deaths. (Tables 1-3)

Curve-fitting equations with a coefficient of determination (r²) of scatter plots of data of increasing daily number of cases and deaths by country were calculated by linear and polynomial analyses. From the graphic peak of the increase in reported new cases and new deaths for each country, curve-fitting equations with a resultant coefficient of determination (r²) of scatter plots of decreasing daily new cases and new deaths were calculated by linear and logarithmic regression analyses. Predicted end-point days (time from each country's peak in new cases and new deaths to the calculated days of completed resolution of new cases and new days) were calculated and a predicted end-date for each country's new daily cases and new daily deaths were derived and reported as predicted conclusion dates for both new cases and new deaths. (Graphs: 1-3, Tables: 2-3)

The number of sites, the physicians enrolled, the patients accrued, and the infusions of convalescent plasma administered were recorded from the June 1, 2020 Mayo Clinic website: Convalescent Plasma (COVID-19 (Coronavirus) Treatment – Mayo Clinic.⁶ This data was recorded and compared with data from the American Hospital Association website⁷ (Graph 4) and the Johns Hopkins database.³

Results: The demographics of these four representative countries reflect the tremendous variability of reported numbers of new daily cases and new daily deaths. ^{3,4} (Table: 1) Total country populations range from Spain and Italy (46.94 million and 60.36 million, respectively), the USA (328 million), and China (1.39 billion). On the date (May 24, 2020) as the endpoint day of this analysis, the reported deaths from China (4,638 deaths) and the USA (97,087 deaths) reflected extremes in mortality-- But the Chinese and the USA mortality rates of reported deaths to reported confirmed cases at that time were similar (5.52% and 5.98%, respectively). Spain (28,678 deaths) and Italy (32,735 deaths) demonstrated mortality rates twice that of China and the USA: Spain 12.19% and Italy 14.27%. At that time (May 24, 2020), the percentage of confirmed cases to the population in the countries of Italy (0.380%), USA (0.496%), and Spain (0.504%) were similar, whereas, China (0.006%) was 100 times less.

While the extent of total country mortality numbers on May 24, 2020 range from China (4,638) to the USA (97,087), the more telling observation is a similar crescendo-decrescendo epidemic pattern displayed by the four countries with regards to reported new daily cases and new daily mortalities. (Graphs 1-2, Tables 2-3) These crescendo-decrescendo patterns graphically demonstrate three phases of herd immunity⁸⁻¹⁸: (1) an initial increasing quadratic (polynomial to the second order) pattern in reported daily new cases and deaths, (2) a peak day, and then a subsequent (3) declining pattern (approximating a logarithmic decline) over time. The resultant linear and logarithmic curve-fitting derived regression equations of the graphic representation of declining pattern scatter plot analysis (phase 3) can roughly predict the endpoint from the epidemic peak (phase 2) of daily reports of new cases and new deaths when y (number of new daily cases or new daily deaths) crosses zero (linear) or asymptotically approximates reaching zero (logarithmic plots). The coefficient of determination (r²) represents the "goodness of fit" of the applied derived curve-fitting equations: linear, quadratic, and logarithmic. As the r² approaches "1", the derived equation suggests a better overall mathematical approximation of the derived equation to the curve-fitting scatter plot and suggests a higher predictability with less variability of the endpoint calculations.

The number of sites, the physicians enrolled, the patients accrued, and the infusions of convalescent plasma administered were recorded from the June 1, 2020 Mayo Clinic website: Convalescent Plasma (COVID-19 (Coronavirus) Treatment – Mayo Clinic.⁶ This data was recorded and compared with data from the American Hospital Association website⁷ and the Johns Hopkins database.³ As of June 1, 2020, through the Mayo Clinic website⁶, there has been a reported accrual of 7,157 physicians, 2,396 sites (44% of acute care hospitals in the USA), 18,543 infusions of convalescent plasma (1.02% of the 1.8 million COVID-19 positive patients) and 24,513 patients enrolled in this research study--5970 accrued patients did not receive convalescent plasma – (e.g. protocol exclusion parameters, improved without treatment, died before infusion, etc.)

Discussion: The logarithmic calculated predicted resolution dates regarding both new cases and new deaths are similar for China, Italy, and Spain. (Tables 2 and 3) Consistent with the significant difference between the slope of the USA regression analyses versus that of the other three countries, the USA demonstrates extremes in predicted resolution of new deaths (approximately 29 months from now) and resolution of new cases of COVID-19 (approximating 9 centuries from now – hopefully a nonsensical outcome prediction).(Tables 2 & 3) These analyses suggest that there is something markedly different in the multifaceted response to the containment and treatment of COVID-19 patients in the USA compared to the other three countries: China, Italy, and Spain. Without this discussion deteriorating into that which Robert Condon, M.D., F.A.C.S. would intimate being the potential for a Type III statistical error (concluding that which is not supported by the data)¹⁹, what is the USA doing differently compared to these three countries?

Imposition of individual quarantine to decrease individual risk of exposure; testing and tracking to identify COVID-19 positive individuals; and supportive and resuscitative methods used in infected COVID-19 individuals—all have been tried by these countries with varying degrees of implementation, compliance, and success. Systematic collections of the increasing COVID-19 PCR-positivity statistics and the progressive morbidity, deaths, and recoveries are being reported daily.³⁻⁴ While the hope for the development of a vaccine looms in the future, little is spoken in the USA of tailoring the medical response to the COVID-19 pathology in regards to the independent variable of *time* which is the x-axis of all these graphs and calculations.

The world is dealing with a virus of which humanity is immunologically naïve; and, when infected, the body responds severely: ARDS, SIRS, and death. 20-22 The world's goal is to find a cure for COVID-19 (family *Coronavirus*, Genus and species: *SARS-CoV-2*)²³ –that is, *the development of a vaccine* 24-25 which is probably months away. At present, the imperfectly-effective methodologies in addressing COVID-19 have been mainly: (1) the clinically passive techniques of prevention utilizing Personal Protective Equipment (PPE), isolation, stay-at-home mandates, and quarantine 26-29; (2) the clinically active (but not completely successful) methodologies of resuscitation and supportive care of failing organ systems in the individual COVID-19 infected patient 30; and (3) promotion of therapies that have unproven effectiveness 31,32, have variable effectiveness and possibly limited availability 33-39, and those that are dangerous and no proven value. 40,41 From the present analysis, the immediate focus of the USA must be to redirect medical treatment to the pattern of that which has been employed differently in China 42-55, Italy 56-58, and Spain. 59

By this analysis, resolution of the COVID-19 epidemic in the USA is not soon forthcoming when compared with China, Italy, and Spain. Instead of a direct offensive approach: Why not flank the virus and set national intermediate goals that use time to our advantage? The USA needs to develop methodologies to lessen both the toxic symptomatology in the COVID-19 infected individual and the host (infected individual) response to the COVID-19 virus--while the process of increasing individual immunization leading to national herd immunity is progressing. The straight-on offensive of developing a vaccine is probably months away. We are fighting a time dilemma comprising the interval of time in developing an individual's immunity to a COVID-19 infection versus development of the severe symptomatology due to viral and internal host-vs-COVID-19 responses. Intermediate new methodologies of the USA should engender

implementing variably-effective, clinically-imperfect therapies and strategies that don't conflict with the goal to develop a "cure." Such intermediate goals with limited serious side-effects should modify, dampen, or delay the immediate COVID-19 pathology and the body's response to the infection of COVID-19.

While the graphs of all four countries predict epidemiologic distribution of the development of and resolution by herd immunity over time, the time required to reach the threshold of herd immunization is important. China's index epidemic in Wuhan, Hubie province, has already reportedly resolved. Possibly due to their countrys' physical sizes, smaller populations, twice the death rates, and stricter "stay-at-home" mandates, resolution of the epidemics in Italy and Spain are predicted by this analysis to occur over this coming summer. If the observed USA trend (a "less negative slope") persists, though, then the predicted resolution in the USA is extreme suggesting two years for the resolution of new deaths and a millennium for complete resolution of new cases (which hopefully is a nonsensical conclusion). The USA's publicly-pronounced focusing on measures of avoidance and isolation containment, testing, and a rush for vaccine development as the first-line methodologies of combating the COVID-19 pandemic has minimized USA utilization of convalescent plasma⁶⁰⁻⁷⁴ in deference to that which was done in China, Italy, and probably Spain.

While we, as a nation, look to the Spanish flu pandemic of 1918 as the historical blueprint⁷⁵ in the promotion of isolation methodologies in the present COVID-19 pandemic, it is the treatment of rabies of which we should emulate in combating COVID-19.^{5,76,77} The encephalopathy of rabies (*Lyssavirus*), with its near-fatal symptomatology, has an almost 100% mortality as untreated rabies at roughly a month from the time of inoculation (a bite by a rabid animal). The 21-day-progressively-more-virulent vaccinations of Louis Pasteur with attenuated virus provided immunity to the individual before the approximate completion of the one-month time interval between inoculation and symptomatic expression. While Pasteur's technique was successful with rabies, he failed attempting to implement a comparable technique in the development of a vaccine for anthrax (*Bacillus anthracis*)⁷⁸ as there was little time-delayed impediment between host inoculation and expression of the disease.⁵

With COVID-19, it is reported that from the time of exposure and infection to initial symptomatology is approximately five days. Yet, the development of immunity after contraction of COVID-19 reportedly requires two weeks. When a previously immunologically-naïve individual turns PCR-positive but has minimal symptoms, that is when immediate provision of passive immunity by convalescent plasma administration is indicated as previously suggested in the literature for COVID-19 and other viruses—not waiting or delaying for when the patient is severely symptomatic or at death's door. Unfortunately, that is the present clinical practice directed by the U.S. Food and Drug Administration (FDA) "Recommendation" guidelines 80-84 and the Mayo Clinic's IRB-approved study in collaboration with the FDA.

Convalescent plasma is not a cure—but an imperfect temporizer. Administration of convalescent plasma early could give limited protection, delay the onset, or mute the host response of severe symptomatology thus providing a window of time for the individual to develop the 14-day protection of systemic immunity. "One study found the serologic response to a recombinant SARS-CoV-2 nucleocapsid: IgM 85.4%, IgA 92.7% (median 5d after the onset of

symptoms), and IgG 77.9% (14 d after onset)."^{79,85} By allowing the infected individual's development of immunity in a normal-progressive, safe fashion, passive immunization may transiently also decrease the extent or period of time of viremia thus diminishing the period of time of contagiousness.^{86,87}

At the national level, there is one underlying difference in the response among these four countries in the policy of distribution of convalescent plasma—that is, immediate provision of passive immunity to newly infected individuals, to allow time for their development of their own immunity (~14 days). All four countries have employed convalescent plasma use in the treatment of COVID-19 positive patients, but the United States of America through the U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (DHHS) has mandated IRB-approved research studies in the provision of the convalescent plasma.⁸³

While such a governmental policy legally distances responsibility of the FDA from possible future litigation involving untoward outcomes, the FDA's mandatory recommendation of inclusion in an IRB-approved research study with restrictive patient-enrollment inclusion and exclusion criteria has delayed and minimized implementation of convalescent plasma administration in the USA. The standard-of-care for the administration of plasma in the USA as directed by the FDA today does not require an experimental protocol that would potentially delay or minimize utilization in daily medical care.

The FDA has absolute statutory control over the collection, processing, and distribution of all blood products provided to America hospitals by the American Blood Banks. In normal times, approximately 28 million units of blood products are administered annually: packed red blood cells, fresh frozen plasma, cryoprecipitate, and platelets. The provision of plasma is strictly regulated by the FDA (1) to ensure safety in administration to the recipient patient and (2) to provide for the timely administration of plasma for indicated disorders, such as: (a) clotting factor abnormalities and (b) during volume resuscitation in the presence of clotting factor dilution--especially in trauma care, e.g.: massive transfusion protocols.

Over the last century, passive immunization in the treatment of viral diseases in non-immune viral-infected individuals have shown benefit especially when administered during the initial period of symptomatology. The present Mayo Clinic IRB-approved convalescent plasma study in collaboration with the FDA provides a well-intentioned, controlled, easy-accessible website to physicians for enrollment. Unfortunately, the very requirement for enrollment in a research study promotes the possibility of patient exclusion and tacitly condones *de facto* withholding-of-care to those individuals that unknowingly present to a physician and/or hospital/site that are not enrolled in the study. It will be scientifically important in the future for the Mayo Clinic, the FDA, and the Centers for Disease Control (CDC) to systematically analyze and report the observed actual effectiveness of convalescent plasma. The majority of the American public is unaware that convalescent plasma exists. The present FDA requirement of 100% research participation for convalescent plasma availability promotes a *de facto* restriction to access to convalescent plasma for all COVID-19 positive patients. This is *de facto* rationing that segregates by disallowing unrecruited sites. Expanded access during a pandemic is arguably considered ethical. Research Participation for convalescent, COVID-19 patients admitted to a hospital that is not

participating in a research protocol provides the inherent likelihood of administratively condoning failure-to-treat due to unawareness of convalescent plasma—both by providers and by the patients.

The Mayo Clinic's website as of June 1, 2020, demonstrates a recruitment plateau of 2,396 sites which is approximately 44% of our nation's 5407 acute care hospitals. (Graph 4) Accordingly, 18,543 individuals have been treated with convalescent plasma across the nation under the Mayo Clinic protocol which is approximately 1.02% of the reported COVID-19 positive 1,811,277 Americans on the Johns Hopkins Dashboard of June 2, 2020. These numbers may be low as some physicians (or institutions) enrolled in the FDA research Investigational New Drug (IND) process separately from the Mayo Clinic study especially in New York where probably desperation initiated independent FDA approved studies from physicians of the New York hospitals and medical schools.⁹⁰ Individual physicians may personally enroll under FDA guidelines (becoming a "research investigator" by completing Form FDA 3926 (https://www.fda.gov/media/98616/download); submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov; and the FDA promises to respond within 4 hours as stated on page 3 of "Recommendation for Investigational COVID-19 Convalescent Plasma | FDA."

Uniquely at the bottom of the same page 3 under **Patient Eligibility** is the following:

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol (https://www.uscovidplasma.org)

Clicking on the "www.uscovidplasma.org" link, one is immediately taken from the official FDA government website to the non-governmental Mayo Clinic website.⁶ The box with the arrow () to the right of the Mayo Clinic website link is itself a link to the FDA disclaimer page (http://www.fda.gov/about-fda/website-policies/website-disclaimer) ⁹¹:

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Thus, the U.S. Food and Drug Administration of the U.S. Department of Health and Human Services has *de facto* disavowed and abrogated legal responsibility and culpability in the administration of convalescent plasma to individual COVID-19 infected patients by demanding absolute physician participation in research studies: either the "independent" physician-researcher with an eIND number/research project personally arranged through form FDA 3926 or through the Mayo Clinic research study. Such an FDA-mandated enrollment in "research studies" is administratively-coerced research contrary to the standard-of-practice in the dispensing of plasma by American Blood Banks as statutorily dictated and completely regulated by the FDA. This is government-sanctioned experimentation by either methodology inadvertently promoting exclusion of unaware/unsuspecting COVID-19 positive individuals. A physician and/or site which has not enrolled by either method in these national "experimental" studies are prohibited from providing convalescent plasma if requested by the patient which relegates the COVID-19 positive patient into a *de facto* control group of the "experimental studies."

The present situation is akin to the government-sanctioned withholding-of-care (penicillin) to black American men of Macon County, Alabama with untreated, latent syphilis in the Tuskegee Syphilis Study (1932-1972). While penicillin became the standard-of-care in the treatment of syphilis by the 1950s, the U.S. Public Health Service withheld penicillin in the Tuskegee Syphilis Study until 1972. Agencies of the US government initiated, continued, and dutifully reported to the US government over forty years regarding the Tuskegee Syphilis Study. The reported very low transfusion rate in the present Mayo Clinic study (1.02%) is suggestive of *de facto* withholding-of-care (convalescent plasma) by default to infected COVID-19 patients across this nation by general lack of national public awareness of the possibility of passive immunization (convalescent plasma) and *de facto* administrative dereliction-to-duty to provide straight-forward, clear, concise guidance and expanded public education regarding all aspects of convalescent serum in the treatment of COVID-19 to the American public by the Food and Drug Administration, U.S. Department of Health and Human Services.

Conclusion: The U.S. Food and Drug Administration has issued recommendations linking exclusively the dispensing of COVID-19 convalescent plasma to mandatory physician participation in research studies by requiring an Experimental Investigational New Drug application (eIND like Form FDA 3926 or the standard investigator statement: Form FDA 1572). The FDA has inadvertently established a discriminatory rationing methodology in the dispensing of COVID-19 convalescent plasma. These requirements override statutory FDA policy ensuring equity for all persons requiring blood products. The U.S. Food and Drug Administration, the U.S. Centers for Disease Control, and the U.S. National Institutes for Health of the U.S. Department of Health and Human Services; the U.S. Congress; and the President of the United States of America have the obligation, responsibility, and authority to promote the availability of COVID-19 convalescent plasma to be dispensed like any other plasma product under the statutory regulations of the U.S. Food and Drug Administration. The withholding or delaying of the administration of plasma in the treatment for any indicated disease (no matter the perceived percentage of effectiveness of the treatment), violates the present standard-of-care to provide plasma by the American Blood Banks to all patients with an indicated disease by a licensed physician in a timely fashion with informed consent as statutorily regulated by the FDA. **COVID-19 convalescent plasma** should be available to every patient diagnosed with active COVID-19 infection which is consistent with previous regulations as put forth regarding transfusion of plasma by the Association of American Blood Banks (AABB) as statutorily regulated by the U.S. Food and Drug Administration, coherent with the Medical Profession's ongoing promise to *Primum non Nocere*, and consistent with the ethical expectations of our Society.

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35.0 212 Table 1 Demographics (1) copy.pdf

Table 1: Demographics by Country				
	China	Italy	Spain	USA
Population	1,393,000,000	60,360,000	46,940,000	328,200,000
Total Confirmed Cases *	84,084	229,327	235,290	1,622,612
% confirm cases of the population	0.006%	0.380%	0.501%	0.494%
Reported	4,638	32,735	28,678	97,087
% mortality of confirmed cases	5.52%	14.27%	12.19%	5.98%
* Johns Hopkins Dashbo	pard, 5/23/2020			

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13 Table 2 Confirmed COVID-19 Cases

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13 Table 2 Confirmed COVID-19 Cases Page 947 of 1266							
Table 2: Confirmed COVID-19 Cases							
	China	Italy	Spain	USA			
Total Cases at 5/23/2020	83,145	229,367	245,239	1,622,663			
Date of initial reported case	January 23, 2020	February 21, 2020	February 28, 2020	March 5, 2020			
Date of Peak cases	February 2, 2020	March 21, 2020	March 25, 2020	April 9, 2020			
Days to Peak	11	30	27	36			
Increasing Daily New Cases	16,107	53,510	49,549	462,963			
Linear Increase	y = 332.7x - 531.93	$y=199.38x - 9e^{+06}$	y = -251.22x + 1682	y = 1145.3x - 8328.7			
Upward slope \triangle (cases / day)	332.7	199.4	251.2	1145.3			
r ² (Coefficent of Determination)	0.65	0.84	0.69	0.92			
Polynomial 2 nd order Increase	$y = 33.761x^2 - 72.433x + 345.86$	$y = 10.273x^2 - 119.09x + 391.77$	$y = 17.464x^2 - 237.77x + 681.49$	$y = 26.075x^2 + 180.56x - 2218.4$			
r ² (Coefficent of Determination)	0.7	0.97	0.85	0.96			
Decreasing Daily New Cases	67,038	175,857	195,690	1,159,700			
Linear Regression	y = -25.339x + 2030.2	y = -87.626x + 5595.4	y = -140.68x + 7537.2	y = -210.17x + 31086			
Downward slope \triangle (cases / day)	-25.34	-87.63	-140.7	-210.17			
r ² (Coefficent of Determination)	0.22	0.93	0.77	0.4			
Predicted days to new cases resolution	80	64	54	148			
Predicted date of new cases resolution	April 23, 2020	May 25, 2020	May 19, 2020	September 6, 2020			
Logarithmic Regression	$y = -1109\ln(x) + 4753.7$	y = -1633*ln(x) + 8001.6	y = -2635*ln(x) + 11559	$y = -2680 * \ln(x) + 33989$			
r ² (Coefficent of Determination)	0.35	0.78	0.74	0.31			
Predicted days to new cases resolution	71	134	80	322,050			
Predicted date of new cases resolution	April 16, 2020	August 3, 2020	June 14, 2020	January 7, 2902			

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14 Table 3 Deaths Due to COVID-19

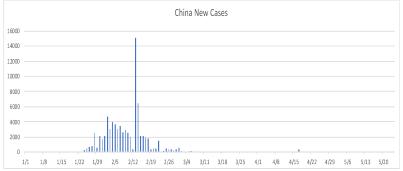
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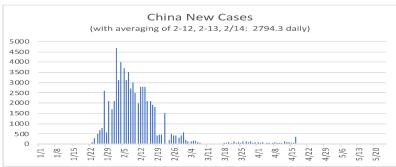
		Deaths Due to COVID-19		Page 949 01 1200
Table 3: Deaths Due to CO	VID-19			
	China	Italy	Spain	USA
Total Deaths at 5/23/2020	4,638	32,162	28,678	96,007
Date of initial reported deaths	January 11, 2020	February 23, 2020	March 5, 2020	March 1, 2020
Date of Peak deaths	February 13, 2020	March 28, 2020	April 3, 2020	April 16, 2020
Days to Peak deaths	□34	35	30	47
Increasing Daily New Deaths	1,368	9,136	10,003	30,985
Linear Increase	y = 4.2998x - 35.011	y = 25.934x - 205.79	y = 37.381x - 245.97	y = 56.686x - 701.21
Upward slope $\triangle(\text{deaths/day})$	4.3	25.93	37.38	56.69
r ² (Coefficent of Determination)	0.69	0.85	0.89	0.65
Polynomial 2 nd order Increase	$y = 0.2234x^2 - 3.5205x + 11.911$	$y = 1.0057x^2 - 10.27x + 17.467$	$y = 1.3467x^2 - 4.3682x - 23.308$	$y = 2.5579x^2 - 66.094x + 301.49$
r ² (Coefficent of Determination)	□0.83	0.95	0.95	0.84
Decreasing Daily New Deaths	3,270	23,026	18,675	65,022
Linear Regression	y = -1.8277x + 89.884	y = -12.173x + 756.99	y = -14.072x + 732.33	y = -33.213x + 2387.2
Downward slope \triangle (deaths/day)	-1.83	-12.17	-14.07	-33.21
r ² (Coefficent of Determination)	0.61	0.86	0.6905	0.34
Predicted days to new deaths resolution	49	59	52	72
Predicted date of new deaths resolution	April 3, 2020	May 27, 2020	May 26, 2020	June 27, 2020
Logarithmic Regression	$y = -37.95\ln(x) + 152.47$	$y = -221.4\ln(x) + 1089.1$	$y = -233.3\ln(x) + 1066.3$	$y = -420.9\ln(x) + 2880.1$
r ² (Coefficent of Determination)	0.64	0.833	0.71	0.33
Predicted days to new deaths resolution	56	137	97	937
Predicted date of new deaths resolution	April 10, 2020	August 13, 2020	July 10, 2020	November 10, 2022

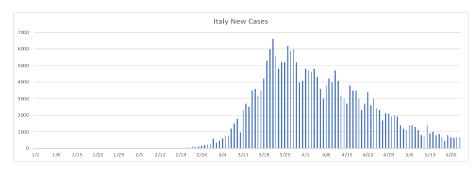
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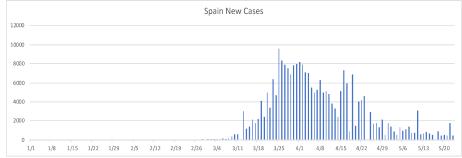
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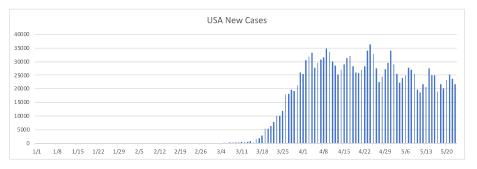
Graphs 1: Daily Plot of New Cases by Country



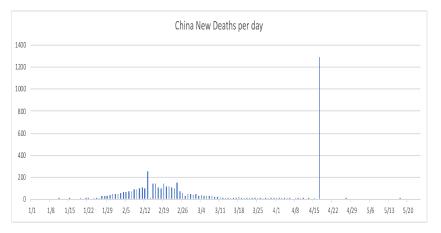




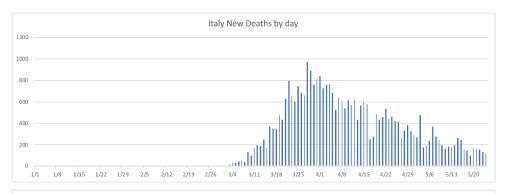


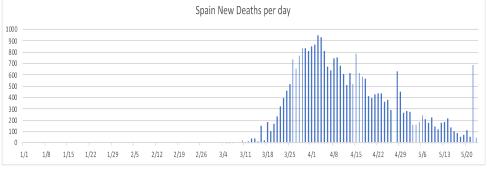


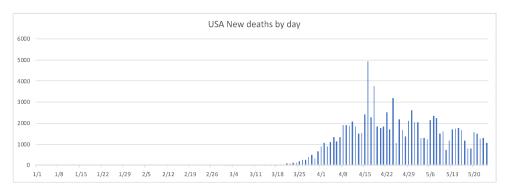
Graphs 2: Daily Plot of New Deaths by Country

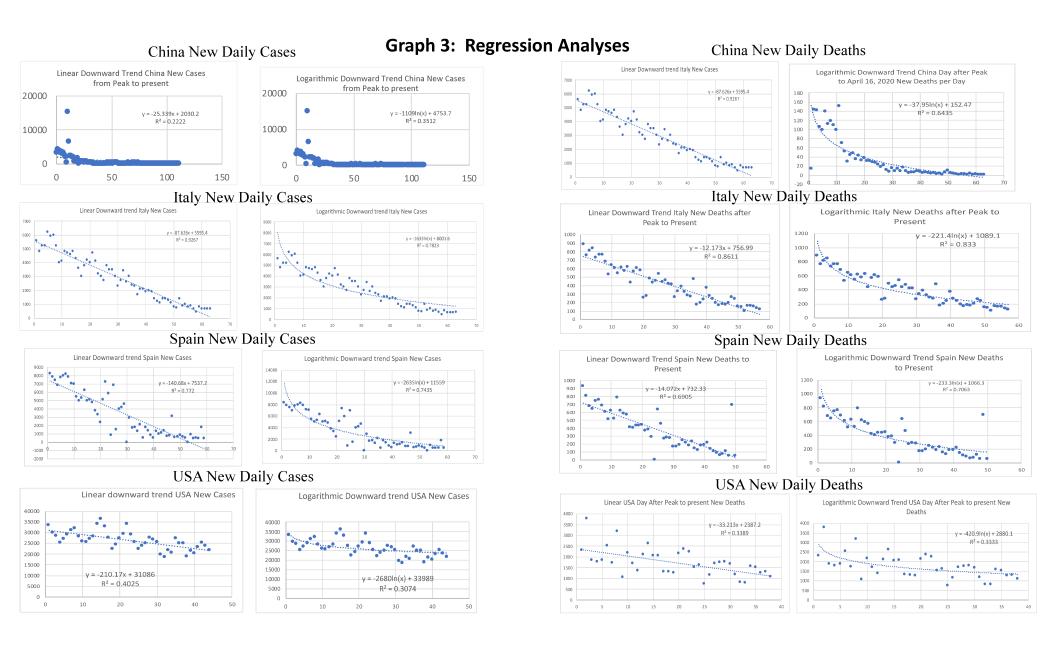






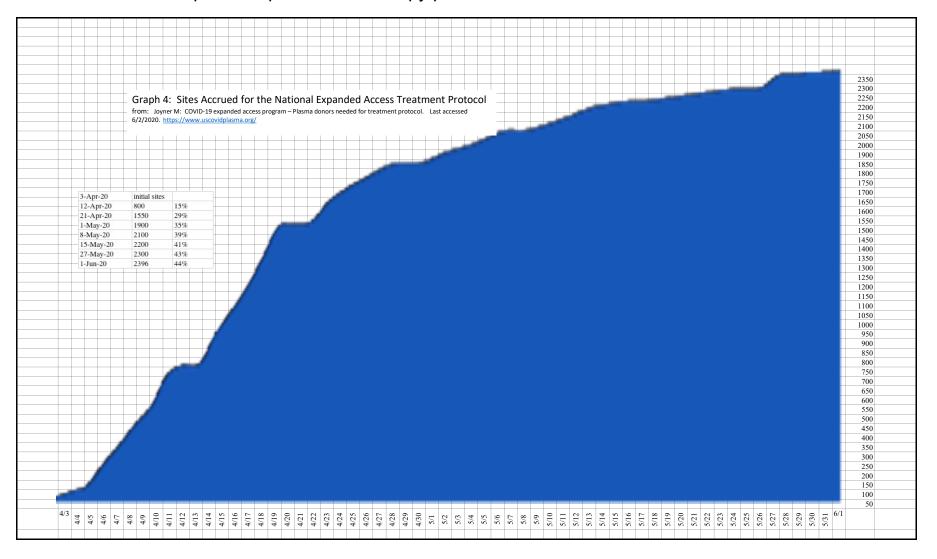






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July 22, 2020

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Re: The Mayo Clinic "Safety Update" should be Classified as a Completed Phase I Trial of COVID-19 Convalescent Plasma

Dear Dr. Fauci and Dr. Hahn:

Passive Immunization has been used safely and successfully in the immediate treatment of many bacterial and viral epidemics in the last 120 years when no definitive drug nor vaccine have been available.²⁻⁴ Passive Immunization through neutralizing antibodies in convalescent plasma has the capacity to modify the intensity of the morbidity and diminish the mortality when used early in the disease process or for prophylaxis in the *immune-naïve* individual. During the present pandemic, COVID-19 Convalescent Plasma⁵⁻¹⁴ has been labelled by the U.S. Food & Drug Administration (FDA) as *Investigational*¹⁵⁻¹⁷ which *de facto* has delayed the collection and application of COVID-19 Convalescent Plasma and stifled the propagation of awareness/knowledge regarding COVID-19 Convalescent Plasma in the Medical Community and in the American public. Until the FDA concludes and declares that the Mayo Clinic Expanded Access "Safety Update" is a *de facto* successful Completed Phase I Trial, labelling COVID-19 Convalescent Plasma as *Investigational*¹⁵⁻¹⁷ will continue to lead to misconception, governmental legal obfuscation, and denial of medical care to individual patients:

1. The misconceptions implying convalescent plasma is an old therapy and thus antiquated, unsafe, and not useful.

- 2. A blurring of the distinction in clinical research between Safety (Phase I Trial) and Efficacy (Phase II and III Trials)
- 3. A blurring of the distinction between Phased Clinical Trials and Expanded Access (Compassionate Use)
- 4. Less-effective use (and potentially ineffective use) of COVID-19 plasma late in the course of the disease when the patient is in extremis rather than for the temporization of the ravages of COVID-19 prior to the individual developing his/her own neutralizing antibodies at approximately two weeks
- 5. No true governmental-directed immediate, active therapeutic plan has been developed due to the fact that the U.S. Department of Health and Human Services (DHHS), most specifically the FDA, has placed disclaimers that the FDA is not responsible in any aspects regarding COVID-19 Convalescent Plasma
- 6. The government has emphasized passive quarantine techniques, medical intensive clinic care support, and long-term goals (vaccines, monoclonal antibodies, etc.) in deference to the short-term temporization possible by administering COVID-19 Convalescent Plasma early in the course of the disease.

How did this present situation come about?

The U.S. Department of Health and Human Service (DHHS)¹⁸ and its multiple components: FDA^{15-17,19}, PHS^{20,21}, NIH²², CDC²³, BARDA²⁴⁻²⁶, etc. have failed to acknowledge to the American people the collective DHHS statutory responsibility and accountability in the complete oversight regarding all aspects of COVID-19 Convalescent Plasma²⁷: collection, testing, availability, and distribution. The FDA websites are strewn with disclaimers negating FDA responsible oversight and accountability listing explicit disclaimers, like: (1) that on page 1 of Investigational COVID-19 Convalescent Plasma: Guidance for Industry¹⁶ (see the reference 16 below for more detail); or (2) by repeatedly-applying in such documents as Recommendations for Investigational COVID-19 Convalescent Plasma¹⁷ the hyperlink which denies and disallows any FDA responsibility or accountability. 28 Yet. on **June 19, 2020**, with the ²⁸ adjacent to the National Expanded Access Treatment Protocol ¹⁷ (the hyperlink to the Mayo Clinic Expanded Access Protocol), The White House²⁹ took full credit for the government's "early" involvement in the Mayo Clinic Expanded Access Safety Study regarding COVID-19 Convalescent Plasma: Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. This Mayo Clinic Safety Study is hyperlinked from the official FDA website¹⁷ as the National Expanded Access Treatment Protocol² ¹⁴ BUT the FDA disavows any FDA involvement, responsibility, and accountability by the FDA disclaimer ² adjacent to it!

The FDA itself doubts and fails to support its own published patient eligibility criteria (this eligibility criteria is for a Phase I Trial) when advising individual physician eIND requests: ¹⁷

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND <u>may want to</u> consider the eligibility criteria used for the <u>National Expanded Access Treatment</u>

Protocol . These criteria includes:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

Contrary to what is being directed by the FDA regarding all these Expanded Access transfusions of COVID-19 Convalescent Plasma, the Mayo Clinic "Safety Update" concludes that COVID-19 Convalescent Plasma is safe and advocates for earlier administration:¹

Given the historical experience that antibody therapies are most effective when given earlier and that convalescent plasma has reduced mortality in prior epidemics, the lower mortality in more recently treated patients would be consistent with greater efficacy from earlier use....Data from the first 20,000 patients transfused with COVID-19 convalescent plasma demonstrate that use of convalescent plasma is safe and carries no excess risk of complications.

The Mayo Clinic's protocol and five other studies [Table I] and all individual eIND requests have been deemed "Expanded Access" by the FDA-that is: "Compassionate Use" only and not Phase I, II, or Phase III trials which is contrary to the statutorily mandated evaluation process of an Investigational New Drug (IND). The intent of Expanded Access is to provide easy availability outside of a trial of an investigational drug or biologic (that has completed a Phase I trial), as is stated in the FDA's description of PL 115-176, Right to Try: 33

For patients with serious or immediately life-threatening diseases or conditions, the FDA remains committed to enhancing access to promising investigations medicines for those unable to access investigational medical products through clinical trials. This is the mission of our <u>expanded access program</u>. The agency is dedicated to these purposes, and it has been for more than three decades.

Unfortunately, "Expanded Access" has become a double-edged sword! Accumulated data from the present Expanded Access protocols—there are 6 such studies of COVID-19

Convalescent Plasma listed [Table I] for the USA in NIH *ClinicalTrials.gov*³⁴ plus the eIND individual applications of COVID-19 Convalescent Plasma <u>are all</u> "Compassionate Use" only and thus not Phased Clinical Trials. As the reported results from the Mayo Clinic "Safety Update" have the patient number of 20,000 (outstanding statistical power for a Phase I study) and extremely low transfusion-related morbidity and mortality so that the FDA <u>should</u> affirm a "Completed Phase I Study" [Table II]— but to do so is contrary to the FDA definitional distinctions between "Compassionate Use" vs. "Phased Trials." This confusion is amplified by the FDA's failure to differentiate between "Safety" (a Phase I Trial) and "Efficacy" (Phase II and III Trials). Having no "Completed Phase I Study" for COVID-19 Convalescent Plasma, the FDA/NIH have officially confirmed ongoing "Efficacy Studies" of COVID-19 Convalescent Plasma (Phase II and III Trials) registered with NIH *ClinicalTrials.gov*. This is the antithesis of the appropriate progression in Phased Trials in the evaluations of a new drug or new biologic. No Institutional Review Board (IRB) would allow this application³⁴ of the principle of "Expanded Access" to continue--BUT, all IRBs are overseen and explicitly regulated by the U.S. FDA.³⁴

Declaring the Mayo Clinic study a <u>Completed Phase I Trial</u> is so important for the American people because once the Mayo Clinic's "Safety Update" is labelled a <u>Completed Phase I Trial</u> then PL 115-176, the Right to Try Law^{33,35}, <u>will permit any person in the United States to request and receive COVID-19</u> Convalescent Plasma <u>at an early phase of their disease</u> (COVID-19 positivity with or without early COVID-19 symptomatology) or <u>prophylactically for high risk individuals</u> in any Emergency Room/Hospital in the nation. If, with presentation to the ER, the patient is refused provision of COVID-19 Convalescent Plasma, that refusal will be a violation of the Right to Try Law, (PL 115-176)^{33,35} and will probably also violate the patient's rights under EMTALA of the Omnibus Act of 1986, (PL 99-272).³⁶

Suggestions:

- 1. The U.S. Food & Drug Administration immediately confirm to the American people that the Mayo Clinic "Safety Update" is a Successfully <u>Completed Phase I Study</u>.
- 2. The Presidential COVID-19 Commission with the aid of its DHHS members should announce organized plans of the Federal Government for the collection, assaying, distribution, and administration of COVID-19 Convalescent Plasma in the prophylaxis and early treatment of COVID-19.
- 3. The Secretary of the U.S. Department of Health and Human Services confirm the full DHHS authority, responsibility, and accountability regarding COVID-19 Convalescent Plasma.
- 4. The U.S. Food & Drug Administration (FDA) oversee, be responsible for, and be completely accountable for all aspects of COVID-19 Convalescent Plasma processing: procurement, assaying for safety, confirm COVID-19 virus negativity, and antibody concentration assessment through the U.S.A. Blood Banks as the FDA is statutorily mandated by the U.S. Congress.

- 5. The U.S. Public Health Service and the U.S. Centers for Disease Control develop a nationwide distribution plan through the hospitals, nursing homes, etc. prioritizing distribution to all individuals at risk. The U.S. Public Health Service and the U.S. Centers for Disease Control reassume full responsibility and accountability for their activities.
- 6. Administration of COVID-19 Convalescent Plasma should be as previously done for all convalescent plasma over the last 120 years: At early-onset of the disease including asymptomatic COVID-19 positive individuals and persons at high risk of exposure.
- 7. If such a plan is not instituted, then the oversight mechanisms in this country hopefully will reestablish and reaffirm their oversight mandates to the American people. The Offices of the Inspectors General (e.g. DHHS, DVA, DOJ, etc.), the Comptroller General, the Attorney General of the United States, the Attorneys General of every state in the nation, and the Congress of the United States of America should ask the following questions:
 - a. Why has the Mayo Clinic "Safety Update" <u>NOT</u> been considered by the FDA as a "Completed Phase I Study"?
 - b. Why are Phase II and Phase III studies underway when a Phase I study has not been completed?
 - c. When any Phase I study is declared "completed" by the FDA, then does not PL 115-176 become applicable?

Respectfully,

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Chief, Unit II (SLU) General Surgery Division
Surgical Service, John Cochran (St. Louis) VAMC

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 Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, et al: Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clinic Proceedings 2020; 95(x): xx-xx. https://www.mayoclinicproceedings.org/article/S0025-6196(20)30651-0/pdf

> Serious Adverse Events. Key serious adverse events (SAE) related to the transfusion of convalescent plasma are reported in Table 2. Our report is not a comprehensive summary of all risks associated with hospitalization of COVID-19 but did assume that convalescent plasma potentially could cause life-threatening cardiac events and thrombotic events, so these were collected with an underlying assumption of attribution. Within four hours of completion of the COVID-19 convalescent plasma transfusion, 146 SAEs classified as transfusion reactions were reported (<1% of all transfusions). Of these SAEs, there were 83 non-mortality events reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction. Of the SAEs reported within four hours of plasma transfusion, there were 63 mortalities (0.3% of all transfusions) and 13 of these mortalities were judged as related (possibly, n=12; probably, n=1; definitely, n=0) to the transfusion of COVID-19 convalescent plasma. Within seven days of completion of the COVID-19 convalescent plasma transfusion, 1,136 other SAEs were reported. Of these SAEs, 87 thromboembolic or thrombotic events were reported, 406 sustained hypotensive events requiring intravenous pressor support were reported, and 643 patients suffered a cardiac event. Notably, the vast majority of the thromboembolic or thrombotic complications (n=55) and cardiac events (n=569) were judged to be unrelated to the plasma transfusion.

(Please see Table II: Mayo Clinic Study morbidity, mortality, and odds of dying which is a data base analysis of the results and why the Mayo Clinic "Safety Update" should qualify as a Completed Phase I.)

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Contains Nonbinding Recommendations

Investigational COVID-19 Convalescent Plasma

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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As the Nation's doctor, I often get asked: What should I do if I think I might have coronavirus? Well, it is important to know the symptoms--they include: fever, cough, and shortness of breath. If you are having these symptoms or worry you might have coronavirus, please call your healthcare provider. We don't want you to go into the ER or the doctor's office without talking to them first because you might spread coronavirus to someone else. They will help you think through and learn how to react including figuring out where to go to get tested if necessary.

Dr. Jerome Adams, PSA, If You Are Sick, March 19, 2020.

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- 26. U.S. Department of Health & Human Services: BARDA's Rapidly expanding COVID-19 medical countermeasure portfolio. https://www.medicalcountermeasures.gov/app/barda/coronavirus/COVID19.aspx
- 27. U.S. Department of Health and Human Services, Food and Drug Administration: FDA News Release: Coronavirus (COVID-19) Update: FDA coordinates national effort to develop blood-related therapies for COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-coordinates-national-effort-develop-blood-related-therapies-covid-19

28. U.S. Food & Drug Administration: Website Disclaimer. https://www.fda.gov/about-fda/website-policies/website-disclaimer

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- 29. McEnany K: White House Press Conference, June 19, 2020. https://www.youtube.com/watch?v=GxX6CgI7RJ4

...Finally, well second, to finally, we are encouraged that we continue to gather positive data on a number of therapeutics: heparin; dexamethasone or steroids as it's more commonly known; convalescent plasma; and Remdesivir have all shown promise in treating coronavirus. Preliminary findings in a large UK-based recovery trial found that when steroids were used there was a 30% reduction in death for coronavirus patients on ventilators. The FDA is reviewing this recovery trial data now. Additionally, on convalescent plasma there's more encouraging news in partnership with mayo clinic the Trump administration move very quickly on this therapy and it's earliest days recognizing that it showed promise. Through the FDA Mayo Clinic and the administration's work in our hand-in-hand partnership, we found that this treatment is very promising--this has shown that the administration has left no stone unturned in looking at every possible treatment at the very early stages. The lead investigator of this Mayo Clinic study, Dr. Michael Joyner, summed up his work in saying that convalescent plasma "continues to look promising" noting the "excellent news of this study which covered a diverse population of patients about 20% were African-American, nearly 35% Hispanic, 5% Asian, and 40% women. Prior experience with respiratory viruses and some data that have emerged globally suggest convalescent plasma has the potential to lessen the severity or shorten the length of the illness caused by COVID-19. The results from the Mayo underscore that promise. As you can see, the Trump administration and FDA led on identifying convalescent plasma as a therapeutic and the results are encouraging...

- 30. U.S. Food and Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma, page 2: **National Expanded Access Treatment Protocol** hyperlink: COVID-19 expanded access Plasma donors needed for treatment protocol. https://www.uscovidplasma.org/
- 31. U.S. Food & Drug Administration: Expanded Access. https://www.fda.gov/news-events/public-health-focus/expanded-access

- 32. U.S. Food and Drug Administration: Investigational (IND) Application. https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
- 33. U.S. Food and Drug Administration: Right to Try. https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try
- 34. U.S. National Library of Medicine: NIH ClinicalTrials.gov. https://clinicaltrials.gov/
- 35. U.S. Food & Drug Administration: Institutional Review Boards (IRBS) and Protection of Human Subjects in Clinical Trials. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/institutional-review-boards-irbs-and-protection-human-subjects-clinical-trials
- 36. U.S. Food and Drug Administration: FDA FACT SHEET: Right to Try. https://www.fda.gov/media/133864/download
- 37. CMS.gov, Centers for Medicare & Medicaid Services: Emergency Medical Treatment & Labor Act (EMTLA) https://www.cms.gov/Regulations-and-Guidance/Legislation/EMTALA

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42.0 322 Table I - Listing of USA Trials on NIHClinicalTrials 7-6-202 (1) copy.pdf

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
1	COVID-19 Convalescent Plasma (CCP) Transfusion	Recruiting	No Results Available	COVID-19	Biological: COVID Convalescent Plasma	University of Mississippi Medical Center, Jackson, Mississippi, United States	Early Phase 1	https://ClinicalTrials.gov/show/NCT04412486
2	Convalescent Plasma for the Treatment of COVID-19	Recruiting	No Results Available	COVID-19	Drug: Convalescent Plasma	Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04389710
3	Treatment With Investigational Convalescent Plasma and Measure Antibody Levels in Patients Hospitalized With COVID-	Recruiting	No Results Available	COVID-19	Drug: Convalescent Plasma	University of New Mexico Health Sciences Center, Albuquerque, New Mexico, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04434131
4	COVID-19 Convalescent Plasma for the Treatment of Hospitalized Patients With Pneumonia Caused by SARS- CoV-2.	Recruiting	No Results Available	COVID-19	Biological: COVID- 19 Convalescent Plasma	Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, United States	Phase 1	https://ClinicalTrials.gov/show/NCT04397757
5	A Trial of CONvalescent Plasma for Hospitalized Adults With Acute COVID- 19 Respiratory Illness	Not yet recruiting	No Results Available	COVID-19	Biological: Convalescent plasma	Weill Cornell Medicine, New York, New York, United States	Phase 3	https://ClinicalTrials.gov/show/NCT04418518
6	Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection	Recruiting	No Results Available	COVID-19	Biological: Convalescent Plasma	Hackensack University Medical Center, Hackensack, New Jersey, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04343755
7	Evaluating the Efficacy of Convalescent Plasma in Symptomatic Outpatients Infected With COVID-19	Not yet recruiting	No Results Available	COVID-19	Biological: CCP	Metro Infectious Disease Consultants, Burr Ridge, Illinois, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04438057
8	Convalescent Plasma as a Possible Treatment for COVID-19	Recruiting	No Results Available	COVID-19	Biological: Convalescent plasma Biological:	University of Illinois at Chicago, Chicago, Illinois, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04442191

22 Table I - Listing of USA Trials on NIHClinicalTrials 7-6-2020 copy

	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
9	Convalescent Plasma as Treatment for Subjects With Early COVID-19 Infection	Not yet recruiting	No Results Available			Hackensack University Medical Center, Hackensack, New Jersey, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04456413
10	Expanded Access to Convalescent Plasma to Treat and Prevent Pulmonary Complications Associated With COVID-19	Available	No Results Available		Biological: Biological: COVID- 19 convalescent plasma	Tulane Medical Center, New Orleans, Louisiana, United States	Expanded Access. Intermediate - size population Treatment IND/Protocol	https://ClinicalTrials.gov /show/NCT04358211
11	Convalescent Plasma for COVID-19 Close Contacts	Recruiting	No Results Available	SARS-CoV 2 COVID-19	_	Columbia University Irving Medical Center/NYP, New York, New York, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04390503
12	COVID-19 Plasma Collection	Recruiting	No Results Available	1	Other: Plasma	Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, United States	N/A	https://ClinicalTrials.gov/show/NCT04344015
13	COVID-19 Convalescent Plasma for Mechanically Ventilated Population	Recruiting	No Results Available	Covid-19	Biological: COVID-	Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, United States	Phase 1	https://ClinicalTrials.gov/show/NCT04388527
14	Convalescent Plasma in ICU Patients With COVID-19- induced Respiratory Failure	Recruiting	No Results Available	Covid- 19 Sars- CoV2	Biological: Multiple Doses of	8700 Beverly Blvd., Los Angeles, California, United States Johns Hopkins University, Baltimore, Maryland, United States	Early Phase 1	https://ClinicalTrials.gov /show/NCT04353206
15	Investigational COVID-19 Convalescent Plasma Infusion for Severely or Life- threateningly Ill COVID-19 Patients	Available	No Results Available		Biological: COVID- 19 Convalescent	Rutgers New Jersey Medical School, Newark, New Jersey, United States University Hospital, Newark, New Jersey, United States	Expanded Access. Individual Patients. Intermediate - size Population	https://ClinicalTrials.gov /show/NCT04420988

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
16	Effects of COVID-19 Convalescent Plasma (CCP) on Coronavirus-associated Complications in Hospitalized Patients	Recruiting	No Results Available	COVID- 19 Sars- CoV2	Biological: COVID- 19 Convalescent Plasma (CCP) Biological: Placebo	San Francisco General Hospital, San Francisco, California, United States UCSF Medical Center at Mount Zion, San Francisco, California, United States University of California, San Francisco Medical Center (Parnassus Campus), San Francisco, California, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04421404
17	Passive Immunity Trial of Nashville II for COVID-19	Recruiting	No Results Available	COVID- 19 Coronavir us SARS- CoV-2	Biological: pathogen reduced SARS-CoV-2 convalescent plasma Biological: Placebo	Vanderbilt University Medical Center, Nashville, Tennessee, United States	Phase 3	https://ClinicalTrials.gov/show/NCT04362176
18	Experimental Expanded Access Treatment With Convalescent Plasma for the Treatment of Patients With COVID-19	Available	No Results Available	COVID Sars- CoV2 Coron a Virus Infection		UMass Medical School, Worcester, Massachusetts, United States	Expanded Access. IND/Protocol	https://ClinicalTrials.gov /show/NCT04445207
19	A Study of COVID 19 Convalescent Plasma in High Risk Patients With COVID 19 Infection	Recruiting	No Results Available	Coronavirus COVID- 19 Convalesc ent Plasma	Plasma	Good Samaritan Hospital, Cincinnati, Ohio, United States Bethesda North Hospital, Cincinnati, Ohio, United States	Phase 2	https://ClinicalTrials.gov /show/NCT04392232
20	A Study Evaluating the Efficacy and Safety of High- Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients With COVID-19 Infection	Recruiting	No Results Available	COVID-19	Biological: anti- SARS-CoV-2 convalescent plasma	Froedtert Hospital, Milwaukee, Wisconsin, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04354831
21	COVID-19 Convalescent Plasma	Active, not recruiting	No Results Available	Coronavirus	Biological: anti- SARS-CoV-2	University of Chicago Medicine, Chicago, Illinois, United States	Early Phase 1	https://ClinicalTrials.gov/show/NCT04340050
22	Convalescent Plasma in the Treatment of COVID 19	Enrolling by invitation	No Results Available	SARS-CoV- 2 COVID Co ronavirus		Trinity Health Of New England, Hartford, Connecticut, United States	Phase 2	https://ClinicalTrials.gov/show/NCT04343261

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
23	Convalescent Plasma for Patients With COVID-19	Recruiting	No Results Available		Biological: Convalescent plasma	Henry Ford Hospital, Detroit, Michigan, United States	Phase 2	https://ClinicalTrials .gov/show/NCT0438 5199
24	Convalescent Plasma for Treatment of COVID-19 Patients With Pneumonia	Recruiting	No Results Available	Corona Virus Infection SA RS-CoV 2 SARS Pneumonia Pneumonia	Drug: High-Titer Anti-SARS-CoV-2 (COVID 19) Convalescent Plasma	University of Virginia Medical Center, Charlottesville, Virginia, United States University of Virginia, Charlottesville, Virginia, United States	Phase 2	https://ClinicalTrials .gov/show/NCT0437 4565
25	Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients	Recruiting	No Results Available	COVID- 19 Coronavir us Coronavir	Biological: Convalescent Plasma Other: Saline solution	Yale University School of Medicine, New Haven, Connecticut, United States Montefiore Medical Center, Bronx, New York, United States NYU Langone Health, New York, New York, United States	Phase 2	https://ClinicalTrials .gov/show/NCT0436 4737
26	Convalescent Plasma in Outpatients With COVID-19	Not yet recruiting	No Results Available	COVID-19	Biological: Convalescent Plasma Biological: Saline	Stanford University, Stanford, California, United States University of Michigan, Ann Arbor, Michigan, United States University of Pittsburgh, Pittsburgh, Pennsylvania, United States Medical University of South Carolina, Charleston, South Carolina, United States	Phase 3	https://ClinicalTrials .gov/show/NCT0435 5767
27	Plasma Therapy of COVID- 19 in Critically III Patients	Recruiting	No Results Available	SARS-CoV Infection	Biological: Convalescent Plasma (anti-SARS- CoV-2 plasma) Biological: Non-convalescent Plasma (control plasma)	Columbia University Irving Medical Center/NYP, New York, New York, United States	Phase 2	https://ClinicalTrials .gov/show/NCT0435 9810

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
28	Human Convalescent Plasma for High Risk Children Exposed or Infected With SARS-CoV-2 (COVID-19)	Recruiting	No Results Available	Corona Virus Infection	Biological: Anti- SARS-CoV-2 Human Convalescent Plasma	Johns Hopkins Hospitals, Baltimore, Maryland, United States	Phase 1	https://ClinicalTrials .gov/show/NCT0437 7672
29	Use of Convalescent Plasma for COVID-19	Not yet recruiting	No Results Available	COVID	Biological: Convalescent Plasma	Northside Hospital, Atlanta, Georgia, United States	Phase 2	https://ClinicalTrials .gov/show/NCT0440 8040
30	SARSCoV2 (COVID-19) Convalescent Plasma (CP) Expanded Access Protocol (EAP)	Available	No Results Available	COVID SAR SCoV2 Convalescent Plasma	SARSCoV2	AdventHealth Orlando, Orlando, Florida, United States	Expanded Access. Intermediate - size Population	https://ClinicalTrials .gov/show/NCT0437 4370
31	Convalescent Plasma vs. Standard Plasma for COVID- 19	Enrolling by invitation	No Results Available	COVID	Biological: Convalescent Plasma Biological: Standard Donor Plasma	Stony Brook University Hospital, Stony Brook, New York, United States	Phase 1 Phase 2	https://ClinicalTrials .gov/show/NCT0434 4535
32	Feasibility Study of Anti- SARS-CoV-2 Plasma Transfusions in COVID-19 Patients With SRD	Recruiting	No Results Available		Drug: SARS-CoV- 2 plasma	Ascension Providence Hospital, Novi Campus, Novi, Michigan, United States Ascension Providence Hospital, Southfield Campus, Southfield, Michigan, United States Ascension Macomb-Oakland Hospital, Warren Campus, Warren, Michigan, United States	Phase 1	https://ClinicalTrials .gov/show/NCT0441 1602
33	Convalescent Plasma Collection and Treatment in Pediatrics and Adults	Recruiting	No Results Available	A Virus	Convalescent Plasma 1 Unit Biological: Convalescent Plasma 2 Units Other: Standard of Care	WVU Medicine, Morgantown, West Virginia, United States	Phase 3	https://ClinicalTrials .gov/show/NCT0437 6034

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
34	Plasma Collection From Convalescent and/or Immunized Donors for the Treatment of COVID-19	Recruiting	No Results Available	COVID-19		National Institutes of Health Clinical Center, Bethesda, Maryland, United States	Observational	https://ClinicalTrials .gov/show/NCT0436 0278
35	ANTIBODY-LEVEL BASED ANALYSIS OF COVID CONVALESCENT SERUM (ABACCuS)	Not yet recruiting	No Results Available	COVID- 19 Severe Acute Respiratory Syndrome (SARS) Coro navirus Infections	19 convalescent plasma	William Beaumont Hospital, Royal Oak, Michigan, United States	Phase 2	https://ClinicalTrials .gov/show/NCT0443 2272
36	CoVID-19 Plasma in Treatment of COVID-19 Patients	Recruiting	No Results Available	COVID 19	Convalescent	The Christ Hospital, Cincinnati, Ohio, United States University Hospitals Cleveland Medical Center, Cleveland, Ohio, United States		https://ClinicalTrials .gov/show/NCT0435 5897
37	Evaluation of SARS-CoV-2 (COVID-19) Antibody- containing Plasma thErapy	Recruiting	No Results Available	COVID Infe ctious Disease		Brigham and Women's Hospital, Boston, Massachusetts, United States	Phase 3	https://ClinicalTrials .gov/show/NCT0436 1253
38	Convalescent Plasma for the Treatment of Patients With COVID-19	Available	No Results Available	COVID- 19 SARS- CoV 2	19 Convalescent Plasma	Children's Hospital Colorado, Aurora, Colorado, United States University of Colorado Hospital, Aurora, Colorado, United States UCHealth Memorial Hospital North, Colorado Springs, Colorado, United States Denver Health Medical Center, Denver, Colorado, United States UCHealth Poudre Valley Hospital, Fort Collins, Colorado, United States UCHealth Highlands Ranch Hospital, Highlands Ranch, Colorado, United States	Expanded Access Treatment IND/Protocol	https://ClinicalTrials .gov/show/NCT0437 2368

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
39	COVID-19 Recovered Volunteer Research Participant Pool Registry	Recruiting	No Results Available	Recovered From COVID-19		Ronald Reagan UCLA Medical Center, Los Angeles, California, United States	Observational No phase listed	https://ClinicalTrials .gov/show/NCT0435 9602
40	CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness (CONCOR-1)	Recruiting	No Results Available	COVID-19	Biological: Convalescent plasma	Brooklyn Hospital, Brooklyn, New York, United States Lower Manhattan Hospital, New York, New York, United States Weill Cornell Medical Center, New York, New York, United States Hamilton General Hospital, Hamilton, Ontario, Canada Juravinski Hospital, Hamilton, Ontario, Canada Juravinski Hospital, Hamilton, Ontario, Canada Condon Health Sciences Centre - University Hospital, London, Ontario, Canada Trillium Health Partners, Mississauga, Ontario, Canada Trillium Health Partners - Credit Valley, Mississauga, Ontario, Canada Trillium Health Partners - Credit Valley, Mississauga, Ontario, Canada Ottawa Hospital - General Campus, Ottawa, Ontario, Canada Scarborough Health Network - General Hospital, Scarborough, Ontario, Canada Scarborough Health Network - General Hospital, Scarborough, Ontario, Canada Scarborough Health Network - Birchmount Hospital, Scarborough, Ontario, Canada Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada Unity Health St. Michael's Hospital, Toronto, Ontario, Canada Toronto General Hospital, Toronto, Ontario, Canada Toronto General Hospital, Toronto, Ontario, Canada Toronto Western Hospital, Toronto, Ontario, Canada Windsor Regional Hospital - Ouellette Campus, Windsor, Ontario, Canada Hotel Dieu Hospital of Lévis, Lévis, Quebec, Canada Hotel Dieu Hospital of Lévis, Lévis, Quebec, Canada Hotel Dieu Hospital, Montréal, Quebec, Canada Centre hospitalier de l'Université de Montréal, Montréal, Quebec, Canada Hotel Dieu Hospital, Montréal, Quebec, Canada Hotel Dieu Hospit	Phase 3	https://ClinicalTrials .gov/show/NCT0434 8656

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
41	Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19	Available	No Results Available	COVID19	Biological: COVID- 19 convalescent plasma	Mayo Clinic in Arizona, Scottsdale, Arizona, United States Mayo Clinic in Florida, Jacksonville, Florida, United States Mayo Clinic Health System in Albert Lea, Albert Lea, Minnesota, United States Mayo Clinic Health System in Austin, Austin, Minnesota, United States Mayo Clinic Health System in Cannon Falls, Cannon Falls, Minnesota, United States Mayo Clinic Health System in Lake City, Lake City, Minnesota, United States Mayo Clinic Health System in Mankato, Mankato, Minnesota, United States Mayo Clinic Health System in Owatonna, Owatonna, Minnesota, United States Mayo Clinic Health System in Red Wing, Red Wing, Minnesota, United States Mayo Clinic Health System - Red Wing, United States Mayo Clinic Health System - Eau Claire, Eau Claire, Wisconsin, United States Mayo Clinic Health System - Franciscan Healthcare, La Crosse, Wisconsin, United States	Population. No phase listed	https://ClinicalTrials .gov/show/NCT0433 8360

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
42	Convalescent Plasma to Limit SARS-CoV-2 Associated Complications	Recruiting	No Results Available	SARS-CoV 2	Biological: SARS-CoV-2 convalescent plasma Biological: Plasma from a volunteer donor	University of Alabama at Birmingham, Birmingham, Alabama, United States University of California, Los Angeles, Los Angeles, California, United States University of California, Irvine Health, Orange, California, United States NorthShore University HealthSystem, Evanston, Illinois, United States Anne Arundel Medical Center, Annapolis, Maryland, United States JHSPH Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States The Johns Hopkins University, Baltimore, Maryland, United States MedStar Washington Hospital Center, Hyattsville, Maryland, United States University of Massachusetts Worcester, Worcester, Massachusetts, United States University of Rochester, Rochester, New York, United States University of Cincinnati Medical Center, Cincinnati, Ohio, United States Lifespan/BrownUniversity (Rhode Island Hospital), Providence, Rhode Island, United States University of Texas Health Science Center at Houston, Houston, Texas, United States	Phase 2	https://ClinicalTrials .gov/show/NCT0437 3460
43	Collection of Anti-SARS-CoV-2 Immune Plasma	Recruiting	No Results Available	Coronavirus Disease 2019 (COVID-19)		University of Miami Infectious Diseases Research Unit, Miami, Florida, United States Bloodworks Northwest, Seattle, Washington, United States	Observational No phase listed	https://ClinicalTrials .gov/show/NCT0434 4977

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	Title	Status	Study Results	Conditions	Interventions	Locations	Phase	URL
44	Convalescent Plasma to Stem Coronavirus (CSSC- 001)	Recruiting	No Results Available		Biological: Anti- SARS-CoV-2 Plasma Biological: SARS-CoV-2 non- immune Plasma	University of Alabama at Birmingham, Birmingham, Alabama, United States University of California, San Diego, La Jolla, California, United States University of California, Los Angeles, Los Angeles, California, United States University of California, Irvine Health, Orange, California, United States MedStar Georgetown University Hospital, Washington, District of Columbia, United States Lee Memorial Health System, Fort Myers, Florida, United States NorthShore University HealthSystem, Evanston, Illinois, United States Anne Arundel Medical Center, Annapolis, Maryland, United States JHSPH Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States The Johns Hopkins University, Baltimore, Maryland, United States University of Massachusetts Worcester, Worcester, Massachusetts, United States University of Rochester, Rochester, New York, United States University of Cincinnati Medical Center, Cincinnati, Ohio, United States Lifespan/BrownUniversity (Rhode Island Hospital), Providence, Rhode Island, United States University of Texas Health Science Center at Houston, Houston, Texas, United States	Phase 2	https://ClinicalTrials .gov/show/NCT0432 3800
45	Acquiring Convalescent Specimens for COVID-19 Antibodies	Recruiting	No Results Available	COVID- 19 Coronavir us Infection Cor ona Virus Infection		Columbia University Irving Medical Center/NYP, New York, New York, United States	Observational No phase listed	https://ClinicalTrials .gov/show/NCT0434 2195

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	n	Cases have	ing received	COVID	-19 CP ar	id followed	post transfi	usion for 7	days
Morbidity (non-mortality	v Serious	s Adverse E	Events [SAE	sl) with	in 4 hour	s of transf	usion due to	transfusio	n:
TACO	37	20,000	0.185%	17					
TRALI	20	20,000	0.100%						
Severe allergic reactions	26	20,000	0.130%						
Total Morbidity (deaths not included)	83	20,000	0.415%						
Deaths due to transfusion	n (within	4 hours of	transfusion	ı):					
Mortality definitely :	0	20,000	0.000%						
Mortality probably :	1	20,000	0.005%						
Mortality probably and possibly:	13	20,000	0.065%						
Total mortality events:	63	20,000	0.315%						
Deaths within 7 days of transfusion completion in Mayo study 4/3-6/2/2020	1136	20,000	5.680%						
Deaths within 4 hours of transfusion in Mayo study 4/3-6/2/2020	63	20,000	0.315%						
Ratios:									
Total Mortality within 4 hours of Transfusion	18.03	to 1 odds of dyi	ng from COVID-	19 vs within	4 hours of tr	ansfusion Conva	alescent plasma		
Mortality probably and possibly due to Transfusion	87.38	to 1 odds of dyi	ng from COVID-	19 vs those	that probably	and possibly die	ed due to transfus	sion Convalescer	nt plasma
Mortality probably due to Transfusion			ng from COVID-						
Table constructed from information	n on pgs 5 a	nd 6 of Ref #1:	Joyner <i>et al</i> : Sa	fety Update	: COVID-19	Convalescent 1	Plasma in 20,000	0 Hospitalized F	atients

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432 Table I Excerpts from WH briefings etc 11-14-2020 copy.pdf

433 Table II Availability of Passive Immunization 11-15-2020 copy.pdf

434 FDA recommendations 11_14_2020 copy.pdf

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542 Appendix 1—Excerpts regarding Passive Immunization (1) copy.pdf

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Appendix G—NIH and FDA responses including establish NIAID Case #12276 6-10-2020 NIH and FDA responses including 6-6-2020 re NIAID Case #12276.pdf

Timeline Bibliography 2021-06-04 Master References

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45.0 01 Dear Members of Congress and President Trump 8_23_2020.pdf

150 Emerald Green Court St. Louis, MO. 63141 314-455-9482

August 23, 2020

Re: Thousands of Americans are *needless dying* because the FDA is illegally ignoring PL 115-176 – The *Right to Try Law*^{1,2} and COVID-19 Convalescent Plasma has <u>NOT</u> been given as Prophylaxis and Early after COVID-19 positivity conversion

Dear Members of the U.S. Congress and President Trump:

By legally, bureaucratic obfuscation and the U.S. Food and Drug Administration (FDA) not officially declaring the Mayo Clinic "Safety Update" a *Completed Phase I study*, the FDA is illegally evading PL 115-176^{1,2} and thousands of Americans are needlessly dying.⁴⁻¹⁰ On March 24, 2020, COVID-19 convalescent plasma was announced by the FDA to the American public:⁴

Convalescent plasma has the potential to lessen the severity or shorten the length of illness caused by COVID-19. This collaboration, involving BARDA, the American Red Cross and the Mayo Clinic , will allow for a simplified process for health care providers about product efficacy. The FDA anticipates that the effort will be able to move thousands of units of plasma to patients who need them in the coming weeks.

Over the last five months ¹⁰, the FDA¹¹⁻¹², The White House¹³, FDA Commission Stephen Hahn, M.D.¹⁴⁻¹⁵, DHHS Secretary Azar¹⁶, and the President^{17,18} have emphasized COVID-19 Convalescent Plasma's importance in the <u>initial treatment</u> and <u>prophylaxis</u> of COVID-19. Since April 3, 2020 to the present, more than five million Americans have contracted COVID-19 and over 160,000 Americans have died. BUT only 1.2% of the COVID-19 infected population has received COVID-19 convalescent plasma through the National Expanded Access Treatment Protocol.^{10,19} COVID-19 convalescent plasma has been <u>incorrectly given to only those</u> <u>severely ill</u> following FDA directed eligibility criteria⁹ rather than to all persons—those severely ill, in early stages of the disease, and prophylactically.⁹ While <u>only 1.2%</u> of the infected COVID-19 population was afforded access to COVID-19 convalescent plasma, when the Chinese came to the aid of the Italians in March 2020, China offered **90 tons of COVID-19** convalescent plasma to the Italian people.²⁰

90 tons x
$$2000$$
 lbs x 454 g x 1 ml plasma x 1 dose = 408,600 doses COVID-19 convalescent plasma

which came from 204,300 individual donations by Chinese citizens recovered from COVID-19.

The one treatment available when patients first contract COVID-19 and for prophylaxis for people of high exposure: healthcare workers, nursing home patients, prisoners, grocery workers, etc. <u>should be</u> COVID-19 Convalescent Plasma. COVID-19 Convalescent Plasma should be given to anyone as soon as they become COVID-19 positive or are placed in a high-risk situation

or environment! Short of a self-contained astronaut's suit for individual quarantine and protection, as COVID-19 is a respiratory-transmitted RNA virus, there is no other absolute preventative method with 100% reliability of avoiding contraction of the disease. As COVID-19 is epidemic throughout the general American population and we are all immunologically naïve to the virus if we have not previously contracted it, we MUST develop immunity (neutralizing IgG antibodies) over a two-week period either by COVID-19 infection or by vaccination. COVID-19 Convalescent Plasma can provide **Passive Immunization** with neutralizing antibodies from COVID-19 recovered patients to immunologically naïve individuals during the two week interval between immunologic naivete and acquired immunity.

As with all convalescent plasmas, the neutralizing antibodies for a specific disease are conveyed by the administration of convalescent plasma. The concept of **Passive Immunization** for which Dr. von Behring was awarded the first Nobel Prize in Physiology or Medicine in 1901, has gone by (and goes by) many names over the last 130 years²³:

- 1) anti-toxins and antisera (e.g.: hyperimmune globulins for tetanus, rabies, etc.)²⁴
- 2) anti-antigen therapy (e.g.: Rhogam)²⁵
- 3) immunotherapy (e.g.: IVIG)
- 4) convalescent plasma (e.g.: measles, mumps, polio, influenza, SARS, Ebola)²⁶

All above are synonyms / variations of **Passive Immunization** and are well-established as <u>early treatments</u> and <u>prophylaxis</u> in diseases in which the human body is immunologically naïve and there are <u>no</u> antibiotic, antiviral, or monoclonal antibody therapies available at the time.²⁷⁻³⁰ Even today, if you have been vaccinated previously with tetanus toxoid in the distant past (>10 years or never at all) and you should step on a nail in a barnyard driving *Clostridia tetani* spores into the plantar space of your foot, you will be given not only a vaccination or booster of tetanus toxoid but also tetanus hyperimmune globulin which is convalescent plasma.²⁴ **Passive Immunization** has been a fundamental teaching in all Internal Medicine and Infectious Diseases courses in all USA medical schools over the last century.³¹⁻³³

By the U.S. Food and Drug Administration (U.S. FDA) designating COVID-19 convalescent plasma "investigational" in March 2020⁴, access to COVID-19 convalescent plasma has been delayed, restricted, and *de facto* rationed to this day--requiring Clinical Research Trials of Phase I (safety) and Phase II/III Efficacy Studies.³⁴ Such a staged Phase I, II, III process is very important in determining any new biologic's safety and subsequent usefulness. Unfortunately, in April 2020, the U.S. FDA immediately implemented a work-around of the entire Clinical Research Trials process by establishing "Expanded Access" (by FDA definition Expanded Access Use = "Compassionate Use" which means it is outside of an appropriate Clinical Trial).³⁵ The FDA workaround directs the physician potentially administering COVID-19 Convalescent Plasma to his/her COVID-19 positive patient to a non-USA governmental site entitled (and is a hyperlink to): National Expanded Access Treatment Protocol⁷ that is a process implemented and administrated by the Mayo Clinic. Adjacent to the National Expanded Access Treatment Protocol is a *little box and arrow* ³⁶ which is a hyperlink/website disclaimer of the U.S. FDA disavowing any responsibility for the National Expanded Access Treatment Protocol³⁶:

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According to another U.S. FDA website, the definition of "Expanded Access" is "Compassionate Use." By definition and practice as directed by the U.S. FDA, patient outcomes, morbidities, and mortalities under the title of "Expanded Access"/"Compassionate Use" of any investigational new drug or investigational new biologic do not qualify for Clinical Trials Research process of Phase I, Phase II, or Phase III studies. Thus, Seven very large COVID-19 Convalescent Plasma Programs listed on the NIH ClinicalTrials website are not eligible for Phase I, II, III research classification at all!: 1) Tulane University; 2) Rutgers New Jersey Medical School; 3) University of California and affiliated hospitals; 4) University of Colorado and affiliated hospitals; and 7) the Mayo Clinic Health System and all recruited National Expanded Access Treatment Protocol hospitals throughout the USA (as of 8/13/2020, 2774 Sites, 13,740 physicians enrolled, 93,887 patients enrolled, and 64,050 units of COVID-19 infused).

Why is this so important?--Because by this legally obfuscated, convoluted process the U.S. FDA has (1) continued high-severity eligibility criteria meant for Phase I trials only. Thus, Phase I trials can never be completed with "compassionate use" administration of COVID-19 Convalescent Plasma and has (2) legally circumvented and disregarded the "Right to Try" law^{1,2} (PL 115-176 Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act signed into law May 30, 2018) by never concluding/declaring a "Completed" Phase I trial. Convalescent plasma for the last 130 years has been and should be administered as soon as possible or as prophylaxis for high risk groups (in COVID-19: elderly, diabetics, hypertensive patients, and immunosuppressed patients); cohorted individuals (e.g.: nursing home patients, dorm and military personnel, prisoners, etc.); and individuals at high risk of exposure (e.g.:

healthcare personnel, first-responders, and persons with public contact and exposure). As the National Expanded Treatment Protocol continues indefinitely in place, "Expanded Access" **INAPPROPRIATELY** relegates the administration of COVID-19 Convalescent Plasma only to hospitalized patients with life-threatening associated presentations⁹:

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol . These criteria include:

- Laboratory confirmed COVID-19
- · Severe or immediately life-threatening COVID-19, for example,
 - o Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
 - lung infiltrates > 50% within 24 to 48 hours
 - o Life-threatening disease is defined as one or more of the following:
 - · respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- · Informed consent provided by the patient or healthcare proxy.

In the St. Louis *Post-Dispatch* August 12, 2020, one of the National Expanded Access Treatment Protocol investigators <u>implied</u> "volunteer" <u>patient coercion is appropriate</u> in ongoing Phase II/III studies³⁸:

Since April, the Trump administration has set aside **more that \$300 million** to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving high-risk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?"

It is very unlikely that any Institutional Review Board (IRB) would agree to such an eligibility mandate with implied coercion which is 1) contrary to the voluntary autonomy of Clinical

Research Trial participants and 2) considered unethical. Ironically, all IRBs in the USA are legally overseen by the U.S. FDA.³⁹

Between April 3, 2020 and August 17, 2020, in the National Expanded Access Treatment Protocol, the Mayo Clinic reports 66,735 units of COVID-19 Convalescent Plasma infused. 40 Between this same interval, 5,162,110 Americans have contracted COVID-19 and 164,439 Americans have died. 19 How many of those that have died could have had their clinical course muted and possibly death prevented by the early administration of COVID-19 Convalescent Plasma?—We will never know. On August 17, 2020, it is reported that 1,865,580 Americans have recovered. 19 Each recovered individual could donate by plasmapheresis twice a week vielding 4 units of COVID-19 Convalescent Plasma per week—If all those individuals donated twice, 7.5 million units of COVID-19 Convalescent Plasma could be collected! With regards to directing the collection, processing, and distribution of COVID-19 Convalescent Plasma, this is accomplishable through the AABB⁴¹ if fully-directed, responsibly by the Federal Government through the U.S. FDA. The Federal Government needs to again become the responsible **National Leader** as is mandated by Federal law and promised to the American people--not emboldening privatization and encouraging a disorganized cabal of political and business factions whose only goals are grabbing the glory, encouraging partisan politics, making money, and putting American lives last in priority. A visible National Drive in the collection and distribution of COVID-19 Convalescent Plasma should be initiated immediately akin to FDR and President Eisenhower regarding polio^{42,43}; JFK and phenylketonuria⁴⁴, and Gerald Ford and the first flu vaccine⁴⁵. Nothing short of this will be successful! Nothing short of this will be effective!

Attached is a letter entitled: *The Mayo Clinic "Safety Update" should be Classified as a* <u>Completed Phase I Trial of COVID-19 Convalescent Plasma</u> sent to Drs. Fauci and Hahn on July 22, 2020 and acknowledged in receipt by the U.S. FDA on July 30, 2020. While it has been submitted twice to the Copyright Office for registration so it can be available to all Members of Congress though the Library of Congress, it has yet to be registered and posted. Thus, I will submit this directly to all the members of Congress individually in the hope that someone will read this material, think about it, and act responsibly. (This with attached letter to Drs. Fauci and Hahn will be submitted to the U.S. Copyright Office of the Library of Congress so it will be available to all Americans. I, Charles H. Andrus, M.D., F.A.C.S., waive and turnover all my copyright "rights" to the United States of American and all its people. Please reprint in any format the reader wishes to utilize!)

Respectfully,

Charles H. Andrus, M.D., F.A.C.S. Professor, Department of Surgery, Saint Louis University School of Medicine

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46.0 02 Dear Members of the US House of Representatives 8_28-2020.pdf

150 Emerald Green Court St. Louis, MO. 63141 314-455-9482

August 28, 2020

Re: This is a cover letter to the Congressional Staffer who will initially read the attached packet. After you read this cover letter, please bring it to your Chief of Staff so he or she might assess the importance of showing it to the Congressman or Congresswoman for whom you work.

Dear Member of the U.S. House of Representatives:

As a representative of your Congressional District's constituency, <u>you have been hoodwinked</u> by the FDA, the NIH, and the DHHS; the scientific clinical research community; and the insurance and the pharmaceutical companies regarding COVID-19 Convalescent Plasma.

- 1. The FDA and the Presidential Coronavirus Taskforce has publicly acknowledged COVID-19 Convalescent Plasma for the last 5 months. They have known that China in aid to Italy in March offered 90 tons of COVID-19 Convalescent Plasma to the Italians. If the physicians on the Presidential Coronavirus Taskforce took their textbooks from medical school off their shelfs and read them, they would find sections and chapters on Passive Immunization and its uses as antitoxins, antiserums, anti-Rh-D antibody (Rhogam), rabies vaccine, etc. which have been used successfully for 130 years and its discovery awarded the Nobel Prize in Medicine or Physiology in 1901.
- 2. By the FDA in March 2020 declaring COVID-19 Convalescent Plasma *Investigational*:
- A. The FDA developed "eligibility criteria" that was meant for Phase I Clinical Trials (only when patients' are at death's-door) for the National Expanded Access Treatment Protocol. COVID-19 Convalescent Plasma has <u>NOT</u> been administered appropriately at the onset of COVID-19 positivity nor prophylactically to high exposure and high-risk individuals.
- B. With FDA establishing the National Expanded Access Treatment Protocol for this Investigational biologic, the FDA has used a quirk in their definition of "Expanded Access" to limit administration of COVID-19 Convalescent Plasma to "Compassionate Use Only." "Compassionate Use" means that any outcomes from administration cannot be used to "Complete" a Phase I Clinical Trial and thus the >70,000 administrations given through the National Expanded Access Treatment Protocol are useless in Completing a Phase I study and the "Right to Try" law (PL 115-176) cannot take effect. Thus, no American who newly converts to COVID-19 positivity can presently receive COVID-19 Convalescent Plasma.
- 3. On July 30, 2020, at the American Red Cross, the President was briefed on COVID-19 Convalescent Plasma. Such a visit makes it look like he was just then being introduced to the concept of COVID-19 Convalescent Plasma. Three weeks later on August 23, 2020 at 5:30 EDT, the President in a White House press conference proclaimed a "National Emergency" thus permitting the FDA to circumvent the Phase I "Completion" requirement regarding an *Investigational drug or biologic* and thus avoid addressing the "Right to Try" law (PL 115-176). There were two subsequent possibilities:
- A. If such a plan was immediately implemented, the President would become the immediate hero as no one else—the FDA, the Congress, etc. –has championed COVID-19 Convalescent plasma before the American public –OR—
- B. As has happened, the Scientific Research Community is calling for "Efficacy Research" without a "Completed" Phase I Study so the "Right to Try" law (PL 115-176) is circumvented. With a disease that has a finite mortality rate like COVID-19, to persist in Phase III efficacy research trials with Placebo Control groups is unethical! When COVID-19 Convalescent Plasma is recognized as the only treatment in early COVID-19 positivity and for prophylaxis, the President again becomes the hero as he championed COVID-19 Convalescent

Plasma first – even though it is five months after the FDA and the Presidential Coronavirus Taskforce acknowledged COVID-19 Convalescent Plasma's importance, and now it is at least six weeks after the European Union has committed to \$340 million Euros for the collection and distribution of COVID-19 Convalescent Plasma.

- 4. Other Ramifications:
 - A. As COVID-19 is still classified as *Investigational*, most Health Insurance companies will not pay for it.
- B. While Congress passed legislation in March authorizing some free COVID-19 testing of individuals, it did not authorize free testing of donated COVID-19 Convalescent Plasma (a blood product for transfusion) thus at least \$1000 will be added to the cost of COVID-19 Convalescent Plasma dose which will not be paid for by Insurance Companies as it is still classified as *Investigational*.
- C. The NIH, the NCI, and the FDA and all Phase II/III Clinical Trials can maintain the *status quo* of requiring **Placebo Controls** in the face of COVID-19 Convalescent Plasma being the ONLY treatment at present-**THIS** is coercion of "Volunteer Subjects" as stated in 3,B above which is **Unethical**. No Institutional Review Board (IRB) of any repute would approve of such a dilemma in Clinical Research **BUT** the oversight of all IRBs in this country is the U.S. Food and Drug Administration (FDA).
- D. All authoritative research scientists calling for more "efficacy" research supporting **Placebo** Controls are actually calling for and condoning withholding of a therapeutic agent from 50% of the American "subjects" akin to the U.S. Public Health Service's Tuskegee Syphilis project from 1932 to 1972 in which Penicillin was withheld from 399 African-American men with syphilis. Such "authoritative" scientific spokesmen have an inherent "conflict of interest" which is in direct inconsistency with the intent of the "Right to Try" law (PL 115-176). The unspoken dilemma is that with the "Right to Try" law (PL 115-176), patients with potentially life-threatening illnesses once a Phase I safety-study is "Completed" should be able to receive any drug or biologic outside of Phase II/Phase III clinical trials without coercion of participation in **Placebo control-based clinical trials.** As such, application of the "Right to Try" law (PL 115-176) *de facto* MANDATES that all Phase II/III/IV Clinical Trials under the auspices of the U.S. Department of Health and Human Services (NIH, NCI, FDA, PHS, etc.) need to be revised, reapproved by IRBs, and that will cost billions of dollars, Euros, etc. **In short, THE RESEARCH COMMUNITY NEVER WANTS the Right to Try Law (PL 115-176) to be implemented and applied!**
- E. While the Research Community never wants the Right to Try law (PL 115-176) to be applied, the Pharmaceutical Industry has taken full advantage of its implications by advertising expensive non-insurance-covered drugs and biologics on TV by stating to the public: "Ask your doctor if _______ is right for you."
- 5. In short, the American public has been disingenuously misinformed for five months regarding COVID-19 Convalescent Plasma. All seats of Members of the U.S. House of Representatives are up for reelection on November 3, 2020. ALL incumbents running for reelection –Republicans, Democrats, and Independent have been posed with dilemmas that have essentially "thrown them all under the bus" by the FDA, the NIH, the Health Insurance companies, the Pharmaceutical Industry, and the President! For without Congressional action regarding COVID-19 Convalescent Plasma immediately, more Americans will continue to die without access to the one known therapy available at present in the early treatment and prophylaxis of COVID-19!

Respectfully,

Charles H. Andrus, M.D., F.A.C.S. Professor, Department of Surgery Saint Louis University School of Medicine

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Appendix C – Copy of letters sent to 537 Congressional offices August 2020

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546 Appendix 3—Ethical Issues (1) copy.pdf

Appendix G—NIH and FDA responses including establish NIAID Case #12276 6-10-2020 NIH and FDA responses including 6-6-2020 re NIAID Case #12276.pdf

Timeline Bibliography 2021-06-04 Master References

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150 Emerald Green Court St. Louis, MO. 63141 314-455-9482

November 17, 2020

Donald J. Trump President, United States of America The White House 1600 Pennsylvania Ave Washington, DC. 20500 (202) 456-1414

Anthony S. Fauci, M.D.
Director of the U.S. NIAID
U.S. National Institutes of Health
U.S. Dept of Health & Human Services
5601 Fishers Lane, MSC. 9806
Bethesda, MD. 20892-9806
Re: Case # 12276

Phone: 301-496-5717 FAX: 301-402-3573 Stephen Hahn, M.D.
Commissioner, U.S. Food and
Drug Administration
U.S. Dept of Health & Human Services
c/o CBER Ombudsman
Center for Biologics Evaluation and
Research (CBER)
10903 New Hampshire Ave, W071-7240
Silver Springs, MD. 20993-0002
Phone: 301-796-8240

Re: A Plea for the Availability and Appropriate Administration of *Passive Immunization* against COVID-19 to All in the USA

Dear Mr. President, Dr. Fauci, and Dr. Hahn:

As I have previously written you over the course of the last nine months^{1,2}, most of the members of the Presidential Coronavirus Task Force and yourself, President Trump, have advocated frequently for COVID-19 Convalescent Plasma donations. (Table I: CCP Transcript Excerpts) While you all have advocated for COVID-19 Convalscent Plasma at the National Federal Level, we have NOT applied the <u>appropriate</u> early treatment by the <u>immediate administration</u> of *Passive Immunization* for all those who have contracted COVID-19 (turned positive).³

All Americans deserve some form of immediate treatment with *Passive Immunization* when they contract COVID-19 as-soon-as-possible as was provided to Governor Christie (the Eli Lilly monoclonal antibody, Bamlanivimab)⁴ and the Regeneron antibody cocktail (REG-COV2) to you, Mr. President.⁵ Those monoclonal antibody preparations and polyclonic COVID-19 Convalescent Plasma are collectively the only <u>treatments</u> (*Passive Immunization*) available <u>once a person has contracted</u> COVID-19 (tested positive for the virus)—even if a vaccine becomes available. As with all the biosimilar agents we have employed since the 1880s (e.g.: rabies vaccine, RhoGam, tetanus hyperimmune globulin, IVIG, antitoxins, antisera, and antivenoms, etc.)^{6,7}, *Passive Immunization* must be administered in a timely fashion within hours of the diagnosis to the affected individual so as to be <u>most effective</u>. As such, *Passive Immunization* has always been by definition <u>an empiric therapy</u>.

Statutorily, all treatments must be verified as safe by the U.S. Food and Drug Administration before clinical efficacy studies (phase II and III clinical trials) can progress. The safety of COVID-19 Convalescent Plasma was demonstrated in greater than 80,000 people in the Mayo Clinic-administered/U.S. Government-funded Expanded Access protocol⁸ in >80,000 people. Unfortunately, as "Expanded Access" is a synonym for "Compassionate Care", the U.S. Food and Drug Administration (FDA) has not declared a completed Phase I Clinical Trial of COVID-19 Convalescent Plasma, and thus PL 115-176: The Right to Try Act^{10,11} has been legally sidestepped. History affirms that the efficacy and relative success of the employment of a safe empiric therapy is retrospectively confirmed in the aggregate. With an empiric therapy that is biosimilar to all other *Passive Immunization* techniques^{6,7}, small site-specific or even multiinstitutional research prospective placebo-controlled clinical trials can be discounted and will never "conclude" efficacy studies in the short run when the agent-administration time is wrong. Such studies will only legitimate inconclusiveness as previously continuing the INAPPROPRIATE ADMINISTRATION AT THE WRONG TIME (in severely ill patients with COVID-19 induced SARS) of COVID-19 Convalescent Plasma--days to weeks after the individual's conversion to COVID-19 positivity. To be maximally effective, all neutralizing antibody treatments should be given within hours of positivity confirmation.

Attached are two documents cataloging our present application of *Passive Immunization* in the treatment of COVID-19: 1) Chart I: a composite algorithm of the FDA mandated recommended treatments from the two existing EUAs (COVID-19 Convalescent Plasma of August 23, 2020 and Eli Lilly's Bamlanivimab) which are *de* facto inappropriately restrictive promoting administration at the wrong time; ^{11,12} and 2) Table II: outlining our capacity as a nation to provide COVID-19 neutralizing antibodies at present. ^{4,5,12-16} Combined, the USA has promises of less than a 20 day supply for the rest of the year of Eli Lilly's monoclonal Bamlanivimab (EUA 11/9/2020) and Regeneron's monoclonal cocktail REG-COV2 when approved (EUA pending). The availability of COVID-19 Convalescent Plasma is much more expansive as every recovered patient can give multiple plasma donations with high titers of polyclonal neutralizing antibodies.

On April 3, 2020, the FDA's restrictive *Eligibility Criteria*^{17,18} was published and was blindly followed and applied all summer. As COVID-19 Convalescent Plasma was the only available agent of *Passive Immunization* for the last 9 months, the FDA mandated a restrictive administrative protocol regarding COVID-19 Convalescent Plasma that was medically, inappropriately **Wrong** and was minimally effective in the treatment of severely sick patients demonstrating SARS. ^{19,20,21} On September 2, 2020, the FDA removed the severity-of-illness inappropriate *Eligibility Criteria*^{17,18} from all FDA documentation *QUIETLY* by electronically overwriting on its Internet websites without vociferously informing the American people of this significant change in mandate – which is tantamount to a dereliction-to-duty and the abrogation of the FDA's statutorily mandated promise to honestly protect the American people. Until September 2, 2020, this faulty *Eligibility Criteria*^{17,18} directed the administration of COVID-19 Convalescent Plasma only when the hospitalized patient was only *in extremis* (when, in the time course of the disease, the viremia has probably resolved and the body's SARS response now was subsequently peaking). Neutralizing antibodies (and remdesevir) are indicated for maximum efficacy as soon as possible to limit/curtail the viremia and minimize the subsequent SARS

pathophysiology and NOT at death's door! ¹⁹⁻²¹ This error in the timely administration of COVID-19 Convalescent Plasma, which **IS MEDICALLY WRONG**, has probably facilitated many of the quarter million USA deaths to date! This medically inappropriate administration *Eligibility Criteria*^{17,18} directed by the FDA from April 3, 2020 to September 2, 2020 (152 days) was:

Patient Eligibility^{17,18}

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the **National Expanded Access Treatment Protocol**⁸ (https://www.uscovidplasma.org/), discussed in section III.A. of this guidance. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - o Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation $\leq 93\%$,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
 - lung infiltrates > 50% within 24 to 48 hours
 - o Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

With the issuing of the EUA for COVID-19 Convalescent Plasma by Rear Admiral Hinton, RN, MS, Chief Scientist of the FDA, on August 23, 2020¹², the limitation to only hospitalized patients at deaths-door was continued and sustained. The FDA's surreptitious-rescinding electronic Internet overwrite^{15,16} of the inappropriately-administration-timed *Eligibility Criteria*^{17,18} on September 2, 2020 without a massive public media notification was 1) a dereliction-to-duty by the FDA and 2) a discriminatory denial of early administration of COVID-19 Convalescent Plasma to patients in the outpatient, nursing home, or assistant living venues by the federal government.

Table II: Available Sources of COVID-19 Neutralizing Antibodies²¹ which is attached outlines the presently published limitations in the aggregate of resources of **Passive Immunization** against COVID-19: 1) COVID-19 Convalescent Plasma^{12,15-18}, 2) Eli Lilly's Bamlanivimab^{4,13}, and 3) Regeneron's REG-COV2 (when an EUA is issued by the FDA).⁵ The attached hierarchical organizational chart: Algorithm of FDA Recommended Treatment of COVID-19 Positivity is an outline of the present FDA published available mandates advanced in the EUAs regarding COVID-19 Convalescent Plasma and Eli Lilly's Bamlanivimab. ^{12,13,15,16} These are

discriminatory towards the thousands in the U.S. to come who will contract (turned positive) COVID-19.

Please Mr. President, bring appropriateness to our implementation of *Passive Immunization* in the fight of COVID-19:

- 1. Remove the restrictions mandated in the FDA EUAs regarding 1) COVID-19 Convalescent Plasma and 2) Bamlanimab for application of appropriate, universal availability in the early administration and prophylactic use **to all** who contract COVID-19 (turn positive) and those at high-risk of exposure,
- 2. Declare an Official National COVID-19 Convalescent Plasma Collection, Processing, and Distribution Process/Protocol through the American Association of Blood Banks (the AABB are entirely regulated by the FDA)^{23,24}, other Blood collection sites, and all hospitals (including civilian availability to non-Veterans in the hospitals of the U.S. Department of Veterans Affairs) and other transfusion/infusion sites throughout the United States, and
- 3. Direct the U.S. Department of Health and Human Services and the U.S. Department of Veterans Affairs for the provision of *Passive Immunization* to the entire American population under the full authority and statutory responsibility of the agencies of the DHHS and DVA—e.g. U.S. Food and Drug Administration, U.S. Public Health Service, U.S. Centers for Disease Control, U.S. National Institutes of Health, U.S. Veteran Health Administration, etc.

As this is my duty to the American people as a federal Physician and Surgeon with more than 23 years-of-service within the Veterans Health Administration of the U.S. Department of Veterans Affairs, I will submit this letter as previously to the Presidential Coronavirus Task Force through Drs. Fauci and Hahn and the U.S. Copyright Office for historical chronological preservation and documentation in the U.S. Library of Congress. 1,2

PLEASE Mr. President, consider my plea to you to "...promote the general Welfare..."²⁵ of our nation by initiating a federal-governmental, organized national COVID-19 Convalescent Plasma drive, dispensing, and administering protocol in all aspects of COVID-19 Convalescent Plasma to provide immediate *Passive Immunization* to all persons that turn COVID-19 positive and for prophylactic protection for those in high risk, high contact positions in the care of COVID-19 positive patients.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S. Physician and General Surgeon, Surgical Service, St. Louis (John Cochran) VAMC Professor, Department of Surgery, Saint Louis University School of Medicine

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 https://web.archive.org/web/20200404213000/https://www.uscovidplasma.org/ (From April 4, 2020), While the nominal title of "National Expanded Access Treatment Protocol" implies that the USA government was directing the process—IT WAS NOT! In fact, the hyperlink: next to the National Expanded Access Treatment Protocol on the April 8, 2020 website version of Recommendations for Investigational COVID-19 Convalescent Plasma is representative of the FDA Disclaimer website disavowing any FDA responsibility regarding the National Expanded Access Treatment Protocol and misrepresenting itself:

Responding to the unprecedented challenge fighting coronavirus disease 2019 (COVID-19), the U.S. Government is supporting a national Expanded Treatment Protocol to collect and provide convalescent plasma to patients in need across the country. Plasma from recovered COVID-19 patients contains antibodies that may help fight the disease.

Working collaboratively with industry, academic, and government partners, Mayo Clinic will serve as the lead institution for the program, registering participating providers and potential patients who may benefit and qualify for this investigational treatment.

Subsequent iterations of the National Expanded Access Treatment Protocol: https://web.archive.org/web/20200407105003/https://www.uscovidplasma.org/ (From October 26, 2020).

- 9. U.S. Food & Drug Administration: Expanded Access. https://www.fda.gov/news-events/public-health-focus/expanded-access
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Submission 09-12-2023 of BOOK1 Dear Mr. President -- COVID-19 and Where we went WRONG

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Table I: Transcript Excerpts and other pertinent references regarding COVID-19 Convalescent Plasma (CCP) in Chronological Order

Table I: Transcript Excerpts from White House Briefings, The President, The Vice President, Members of the Presidential Coronavirus Task Force, etc. and pertinent other references in Chronological Order

3/19/2020: https://www.whitehouse.gov/briefings-statements/remarks-president-trump-update-nations-coronavirus-testing-strategy/

The Vice President: But you also challenged us and you challenged American industry to bring the full power and innovation of the American economy to bear on this moment. And whether it be PPE, where we forged a partnership to see to the delivery and the manufacture of hundreds of millions of personal protective equipment; whether it be how we started with 15,000 ventilators in the Strategic National Stockpile — and today, in partnership with GE Healthcare, Ford, and General Motors, we have over 150,000 ventilators in the Strategic National Stockpile; whether it be the extraordinary progress on therapeutics — remdesivir, convalescent plasma — that are literally saving lives; or whether it be, as you reflected, Mr. President, on our steady progress toward achieving a safe and effective vaccine before the end of this year, it's been that public-private partnership that you've led that's made these advances possible.

3/19/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-task-force-briefing-transcript-march-19-trump-takes-shots-at-the-media

Dr. Steven Hahn: (25:42)

Let me give you another example. There's a cross agency effort about something called convalescent plasma. This is a pretty exciting area, and again this is something that we have given assistance to other countries with as this crisis has developed, so FDA has been working for some time on this. If you've been exposed to coronavirus and you're better, you don't have the virus in your blood, we could collect the blood. Now, this is a possible treatment. This is not a proven treatment. Just want to emphasize that. Collect the blood, concentrate that and have the ability, once it's pathogen free, that it's virus free. Be able to give that to other patients and the immunoglobulins, the immune response could potentially provide a benefit to patients.

3/24/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-task-force-briefing-transcript-march-24

Dr. Tony Fauci: (<u>19:45</u>)

And then thoroughly just one, one just comment about drugs and the testing of drugs. You know, you heard yesterday about drugs being out there that physicians on an off-label way can prescribe it to give people hope of something that hasn't been definitively proven to work, but that might have some hope. I don't want anybody to forget that simultaneously with our doing that, we're also doing randomized clinical trials on a number of candidates. You've heard about candidates, but there are others in the pipeline where we'll be able to design the study, and over a period of time, particularly since we have so many infections, we'll be able to determine definitively, are these safe and are they effective? We're talking about Remdesivir, other drugs, Immune Sera, Convalescent Serum, Monoclonal antibodies. All of these are in the pipeline now, queuing up to be able to go into clinical trial, so I'll stop there and [inaudible 00:09:39].

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Table I: Transcript Excerpts and other pertinent references regarding COVID-19 Convalescent Plasma (CCP) in Chronological Order

3/29/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-task-force-briefing-transcript-march-29-trump-extends-task-force-guidelines-to-april-30

Donald Trump: (04:58)

We will ensure that we can give cities and states the best information to guide local decision makers in making. I want to point out that the hydroxychloroquine is being administered to 1,100 patients, people in New York along with the Z-Pak, which is azithromycin, and it's very early yet. It's only ... It started two days ago, but we will see what happens. I want to thank Steven Hahn, who's a great doctor. Left one of the best jobs in our country running an incredible hospital in Texas, and he's the head of the FDA and Steven got approval for that so fast. Let's see how it works. It may, it may not, but we may have some incredible results. We're going to know soon. So it's tested ... It's being tested on 1,100 people in New York. The FDA is also allowing the emergency use of a blood-related therapy called convalescent plasma as an experimental treatment for seriously ill patients.

3/30/2020: https://www.whitehouse.gov/briefings-statements/remarks-president-trump-vice-president-pence-members-coronavirus-task-force-press-briefing-14/

The President:

The FDA is also allowing the emergency use of a blood-related therapy called convalescent plasma as an experimental treatment for seriously ill patients. This treatment involves taking blood plasma from patients who have already recovered from the virus. So they've recovered; they're strong. Something was good in them that worked. And so we take the plasma from those people that have recovered so well — meaning, their plasma is rich in antibodies against the virus — and transfusing it into six [six] patients — sick patients, very — very, very powerfully.

3/31/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-task-force-briefing-transcript-march-31-painful-weeks-ahead

Dr. Fauci: (01:20:30)

Thank you Mr. President. But just for a second before the vaccine, in answer to your question, Steve. There are a number of candidates. The drugs that are now being looked at in various ways, either compassionate use, clinical trials, are generally drugs that already exist for other things. There's a whole menu of drugs and interventions that are now going into clinical trials that are not approved for anything yet. I mean, for example, things like immune serum, convalescent plasma or hyper immune globulin or monoclonal antibodies, a variety of other things. Right now there's a lot of activity going on behind the scenes in the design of the kinds of clinical trials that will give us an answer, because you need an answer, because if it doesn't work, you want to get it off the table and go to the next one. So there are a lot of things.

4/1/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-task-force-briefing-transcripts-april-1

Dr. Fauci: (01:06:46)

You know, John, I don't know, specifically, this individual what they're doing, but I can tell you there's a lot of activity that is centered around a passive transfer of antibodies in the form of convalescent plasma, one. The number is to get immune globulin that you precipitate out of the plasma, and another is monoclonal antibody.

4/4/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-task-force-transcript-april-4

Dr. Hahn: (29:15)

One other thing I'd like to mention is that we, on Friday, stood up a formal

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convalescent plasma program. We have a great deal of enthusiasm for that. There are some reports that this is of benefit to patients in other countries who have had the COVID-19 virus. And what this means is taking plasma from patients who've had the virus and who have recovered, and transferring the immunity, the immunoglobulins if you will, the immunity from that person to someone who's sick. And we're, hopefully, expanding that across the country. The Red Cross is involved in that program and I think it shows a great promise. It needs to be studied like other things, but just like I said before, it provides hope. We don't want to provide false hope, but definitely hope. Thank you.

4/13/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-april-13

Donald Trump: (46:07)

Scientists are also pursuing a blood therapy known as a convalescent plasma, convalescent plasma. This therapy uses antibodies from the blood of recovered patients to treat those who are sick, and this is something that actually is a very old procedure, but it's done in a very modern way.

4/14/2020: https://www.whitehouse.gov/briefings-statements/remarks-president-trump-vice-president-pence-members-coronavirus-task-force-press-briefing-25/

The President

Scientists are also pursuing a blood therapy known as convalescent plasma. Convalescent plasma. This therapy uses antibodies from the blood of recovered patients to treat those who are sick. And this is something that actually is a very old procedure, but it's done in a very modern way.

4/15/2020: https://www.whitehouse.gov/briefings-statements/remarks-president-trump-vice-president-pence-members-coronavirus-task-force-press-briefing-26/

The President

They include antivirals, and also — and they — something which is incredible: It keeps the virus from multiplying. A mechanism that keeps the virus from multiplying. Immune therapies that prevent the immune system from overreaching to the virus. And convalescent plasma treatments that use antibodies from the blood of recovered patients.

The Vice President

When we think of more than 619,000 Americans having tested positive, more than 45,000 having recovered, we wanted to announce today that the FDA recently announced efforts to facilitate the development and access to convalescent plasma, Mr. President. You've spoken about this. People who have recovered from the coronavirus have antibodies in your bloodstream that can attack the virus.

The Mayo Clinic today is working with the Red Cross to make sure that coronavirus patients have access to the convalescent plasma treatments, and over 1,000 institutions across America have already joined this program.

4/15/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-briefing-transcript-april-15

Donald Trump: (<u>07:14</u>)

They include the antivirals, and they have something which is incredible, keeps the virus from multiplying. A mechanism that keeps the virus from multiplying. Immune therapies that prevent the immune system from overreaching to the virus, and convalescent plasma treatments that use antibodies from the blood of recovered patients.

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4/16/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-briefing-transcript-april-16

Donald Trump: (14:35)

We are also encouraging states to work together to harmonize their regional efforts. We'll have numerous cases where states have worked and we'll be working very closely together. As we reopen, we know that there will be continued hardships and challenges ahead. Our goal will be to quickly identify and address any outbreaks and put them out rapidly. If the virus returns in the fall as some scientists think it may, possibly, these guidelines will ensure that our country is up and running so that we can likewise put it out quickly. At the heart of our strategy is the vital role of medical research, especially for therapies that will significantly improve outcomes for high risk patients and reduce the need for urgent care. This will be tremendously valuable in allowing life to eventually return to normal. At least 35 clinical trials are already underway including, antiviral therapies, immune therapies and blood therapies in the form of convalescent plasma.

4/21/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-april-21

Donald Trump: (25:19)

The FDA has now authorized more than 50 diagnostic tests, including, as of late last night, the first test that a patient can take home. You can take it at home, and it's highly accurate. LabCorp intends to make the home collection kits available to consumers in most states, with a doctor's order, in the coming weeks. We also have four different antibody tests already authorized. Tests will help identify individuals who can donate convalescent plasma, thus providing potentially lifesaving antibodies to American patients.

4/22/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-april-22

Donald Trump: (37:49)

My administration has directed more than \$7 billion in federal funding to support the development of treatments, diagnostics, and therapies. And that's something, doctors, I hope you can really work on. It's something so powerful and so important. The FDA, the NIH and industry leaders are establishing master clinical trial protocols to test multiple promising new drugs at the same time. And we're doing a lot of testing right now. More than 1600 locations across the country have signed up to administer convalescent plasma to patients, infusing them with antibodies of those who have recovered. And when they recover, I said it last time, practically the first thing they say is, "I want to give my blood so that I can help other people." They want to give that blood. It's incredible. They're laying in bed, they're still in pretty weakened conditions and they say, "I want to give my blood." And that's happening all the time, isn't it?

4/23/2020: https://www.whitehouse.gov/briefings-statements/remarks-president-trump-vice-president-pence-members-coronavirus-task-force-press-briefing-31/

The President

As we continue to develop potential therapies, the FDA has recently begun a national effort to expand access to convalescent plasma donated from the blood of those who have recovered from the virus. The blood of these donors contains antibodies that can potentially reduce the severity of the illness in those who are sick — and frankly, those that are very sick. Nearly 3,000 patients are now enrolled in the Expanded Access Program, receiving transfusions nationwide.

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And I want to thank all of the people that recovered, for what they've done. They — as I said yesterday, they raise their hand when they barely can walk, and they're saying, "I want to donate blood. I want to donate whatever it is that you want, because we want to help people." It's really quite incredible.

Convalescent plasma will also be used to manufacture a concentrated antibody treatment that does not have to be matched with a particular blood type. This concentrated antibody treatment could be used as a preventative measure to keep healthcare workers and other high-risk populations from contracting the virus in the first place. A very big deal.

4/23/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-april-23

Donald Trump: (<u>10:49</u>)

As we continue to develop potential therapies, the FDA has recently begun a national effort to expand access to convalescent plasma donated from the blood of those who have recovered from the virus. The blood of these donors contains antibodies that can potentially reduce the severity of the illness in those who are sick. And frankly, those that are very sick. Nearly 3000 patients are now enrolled in the expanded access program receiving transfusions nationwide, and I want to thank all of the people that recovered for what they've done. As I said yesterday, they raise their hand when they barely can walk, and they're saying, "I want to donate blood, I want to donate whatever it is that you want, because we want to help people." It's really quite incredible. Convalescent plasma will also be used to manufacture a concentrated antibody treatment that does not have to be matched with a particular blood type.

4/24/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-april-24

Dr. Hahn: (10:53)

And just finally, when it comes to therapeutics, we are leaving no stone unturned in finding treatments for COVID-19. You do know that we don't have any approved currently therapeutics for COVID-19, but we are actively involved with both the academic and the commercial and private sector to find those 72 trials of therapeutics are underway in the United States under FDA oversight and 211 are in the planning stages. So we expect to see more, this includes convalescent plasma as well as antiviral therapies.

6/19/2020: Press Briefing by Press Secretary Kayleigh McEnany, James S. Brady Press Briefing Room, *The White House*. https://www.whitehouse.gov/briefings-statements/press-briefing-press-secretary-kayleigh-mcenany-061920/

Kayleigh McEnany

Finally — well, second to finally, we are encouraged that we continue to gather positive data on a number of therapeutics. Heparin, dexamethasone — or steroids, is as it's more commonly known; convalescent plasma; and remdesivir have all shown promise in treating coronavirus. Preliminary findings in a large, UK-based recovery trial found that when steroids were used, there was a 30 percent reduction in death for coronavirus patients on ventilators. The FDA is reviewing this recovery trial data now.

Additionally, on convalescent plasma, there is more encouraging news. In partnership with Mayo Clinic, the Trump administration moved very quickly on this therapy in its earliest days, recognizing that it showed promise. Though the — through the FDA,

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Mayo Clinic, and the administration's work and our hand-in-hand partnership, we've found that this treatment is very promising. This has shown that the administration has left no stone unturned in looking at every possible treatment at the very earliest stages.

The lead investigator of this Mayo Clinic study, Dr. Michael Joyner, summed up his work, in saying that convalescent plasma, quote, "continues to look promising," end quote, noting the, quote, "excellent news" of this study, which covered a diverse population of patients. About 20 percent were African American, nearly 35 percent Hispanic, 5 percent Asian, and 40 percent women.

Prior experience with respiratory viruses in some data that have emerged globally suggest that convalescent plasma has the potential to lessen the severity or shorten the length of the illness caused by COVID-19. The results from Mayo underscore that promise.

As you can see, the Trump administration and FDA lead on identifying convalescent plasma as a therapeutic and the results are encouraging.

6/26/2020: https://www.rev.com/blog/transcripts/mike-pence-dr-fauci-coronavirus-task-force-press-conference-june-26

Dr. Deborah Birx: (29:18)

We also have new therapeutics that have been used both as compassionate use, like convalescent plasma, and now Remdesivir that we just reallocated and ensured it was available to these States that are facing the increased hospitalization, as well as the monthly allocations that we have been sending out.

Alex Azar: (50:16)

The fifth and sixth elements of this strategy are thanks to the president's Operation Warp Speed. We now have promising therapeutics that are benefiting tens of thousands of American patients and, in all likelihood, have already saved thousands of lives. We've identified two very promising pharmaceutical treatments, Remdesivir and Dexamethasone. As of today, we've allocated more than 120,000 courses of Remdesivir to all of the 50 states. We've added Dexamethasone, a very low cost steroid, to our treatment guidelines. And we believe it's reasonable to assume that other corticosteroids, which may be more readily accessible in some places, would have similar immunological effects. Another promising therapeutic, convalescent plasma, has been used treat more than 25,000 Americans in nearly 3000 sites across the country. There are no certainties in science, but with more than 140 clinical trials underway in the U.S. it's a pretty safe bet that more good news on therapeutics is on the way and on the way soon.

6/28/2020: Stracqualuris V: Secretary Alex Azar on Jake Tapper Show: 'Window is closing' for US to get coronavirus under

control, Trump's HHS Secretary Warns.' CNN

https://www.cnn.com/2020/06/28/politics/hhs-alex-azar-coronavirus-rise-in-cases-cnntv/index.html

6/30/2020: https://www.whitehouse.gov/briefings-statements/press-briefing-vice-president-pence-members-coronavirus-task-force-rockville-mdxz/

Dr. Hahn:

But our work isn't done; more is in the pipeline. As I mentioned, over 25,000 patients in the United States have been treated on our expanded access convalescent plasma program. Now, just as a reminder, that's where we take antibodies — the antibodies that are naturally developed by someone who has gotten the COVID-19 virus and then has recovered — and then we administer that to someone who's sick with COVID-19.

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Secretary Azar:

You heard Admiral Polowczyk talk about how we are better supplied than what we were. Doesn't mean that it's mission accomplished, but we are in a much better place now with PPE and with other supplies. With steroids, remdesivir, and convalescent plasma, if you get COVID-19, we are in a much better position to get you out of the hospital safely.

7/16/2020: https://www.whitehouse.gov/briefings-statements/press-briefing-press-secretary-kayleigh-mcenany-7-16-2020/

Kayleigh McEnany:

And finally, on the therapeutics front, I just want to note: A very encouraging Regeneron contract. A \$450 million contract for a monoclonal antibody cocktail. This is a bioengineered version of convalescent plasma, one of the several therapeutics available to treat COVID. It can be used for prophylaxis and treatment. And they say they could have up to 70 to 300 thousand doses — vials of this by the end of the summer or early fall.

7/30/2020: Remarks by President Trump in a Roundtable on Donating Plasma, American Red Cross National Headquarters. https://www.whitehouse.gov/briefings-statements/remarks-president-trump-roundtable-donating-plasma/

American Red Cross National Headquarters Washington, D.C.

3:01 P.M. EDT

THE PRESIDENT: Thank you very much. Thank you very much, everyone. It's a great honor. It's a magnificent building, and they do a magnificent job at the Red Cross. I'm delighted to be here to discuss the remarkable progress being made in the development of plasma. Plasma. So important. Therapies.

These therapies transfuse powerful antibodies from the blood of recovered patients to help treat those battling the current infection that we all know so well. Plasma is one of the more delicate ways of doing things. It's had tremendous response so far — we've had. And it's an effort to accelerate — to really accelerate new therapies and further reduce mortality.

We've been able to show some tremendous things. If you notice today, it was covered very well. A lot of countries where they thought they were doing well, they're not doing well at all. They've had explosions — explosions, unfortunately.

We're joined by Secretary of Health and Human Services, who's doing a terrific job, Alex Azar. Alex — hi, Alex. FDA Commissioner Stephen Hahn. Hi, Steve. Surgeon General Jerome Adams. And I hope your wife is okay, Jerome. I know she had a little difficulty, but I'm sure she's going to be fine, right? Please give her my regards. Thank you, Jerome. Dr. Francis Collins, who everyone knows — Francis, thank you very much. NIH. And Dr. Anthony Fauci. Anthony, hi. And Deborah. Where's Deborah? Deborah? Hi, Deborah. Good job.

You know, everybody is — everybody is doing a good job. Everybody is working very hard.

I want to also thank to the CO-— CEO of American Red Cross, somebody who's done outstanding work — I've known about it for a long time — Gail McGovern. Thank you, Gail. Really, an outstanding job, too.

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CEO of America's Blood Centers, Kate Fry. Hi, Kate. Thank you very much. CEO of CSL Limited, Paul Perreault. Paul, thank you very much. Great job. And CEO of LabCorp, Adam Schechter. Thank you, Adam, very much.

We've taken bold actions to give Americans access to plasma therapies. The FDA made the treatment available to patients with life-threatening infections beginning in March. We provided \$48 million to the Mayo Clinic to support their expanded access program for plasma. We're providing up to \$270 million to the Red Cross and America's Blood Centers for the collection of up to 360,000 units of plasma.

My administration is partnering with commercial labs, insurers, and healthcare providers to encourage those who have had the virus to donate plasma. So if you've had the virus, if you donate, it would be a terrific thing. We really need donations of the plasma. To those that have had the virus, you've gotten through it, and I guess that means you have something very special there. Right, Gail? So we would appreciate that. It would help a lot of people.

We're grateful to LabCorp for offering free antibody testing to identify people who can donate. And LabCorp has really been fantastic in a lot of ways — other ways also.

As a result of these initiatives, we've already treated nearly 50,000 patients with plasma. Roughly 2 million Americans have fully recovered from the virus. This afternoon, I'm asking these citizens to go to the Coronavirus.gov — it's Coronavirus.gov — and volunteer to donate plasma as soon as you can. We have a lot of people that would heal, would get better. As soon as you can, please.

In addition, I'm once again urging all Americans to protect the elderly, socially distance, wear a mask when you cannot avoid the crowded places. And if you can, you have to avoid crowded places. It just seems like so many things are taking place in crowded places. We don't want that. And always wash your hands — wash your hands as often as you can. Together, we'll defeat the virus, we'll defeat the invisible enemy.

I want to thank the American Red Cross. I've been a fan of the Red Cross for a long time, as you know, and we appreciate the great work that you do. Thank you very much, Gail.

And now I'd like to ask Gail to say a few words, please. Thank you.

MS. MCGOVERN: Mr. President, thank you so much for joining us today and for shining a light on the critical need for convalescent plasma. I'm honored to be seated here with these distinguished, top medical experts who are striving to help us deal with this terrible pandemic. And I am so grateful that the American Red Cross can actually play a role in the treatment of COVID-19.

We're helping to collect units of convalescent plasma, which I've been told is showing promising results, and it's treating COVID patients. We've shipped over 24,000 units so far, and I am in awe of our donors who are donating convalescent plasma. They struggled through this disease, they came through the back end, they have precious antibodies, and hospitals are transfusing their plasma into patients that are struggling mightily with the disease themselves.

And it's a testament to the generosity of the American public. These donors have recovered from a debilitating disease, and they're willing to lend an arm to help somebody they probably will never even have the opportunity to meet. And, in fact, blood donors in general are just so generous. They are helping save someone's life, and they do it without question. And it's just an amazing, amazing thing.

Americans always step up, whether it's a pandemic or a hurricane. And it's a privilege to be able to see the generosity of the American public over and over again, whether they're volunteering, donating blood, or even providing us with financial donations.

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So on behalf of the entire American Red Cross, I want to extend a heartfelt thank you to the people that actually recovered from COVID-19 and are giving this remarkable gift of life to help them recover as well.

And right now the demand for convalescent plasma is exceeding our collections, so we really do need people to come out and donate. In fact, over the past month, the number of orders doubled from our hospitals.

So please, please — I know I speak on behalf of Kate as well — consider donating plasma if you've had COVID, because you are going to do a wonderful thing. It's easy, it doesn't take a lot of time, and I can tell you that when you donate blood and you leave our blood center, you feel so great. You just feel so great about yourself because you just saved someone's life, and not a lot of people can make that claim.

So thank you again, Mr. President. We really appreciate the shout-out for convalescent plasma.

THE PRESIDENT: Thank you, Gail. Great job.

MS. MCGOVERN: Thank you.

THE PRESIDENT: You're really doing something very special. Thank you.

Alex, please.

SECRETARY AZAR: Well, Mr. President, thank you so much for leading the effort now to get people to donate convalescent plasma. This is going to be a major national initiative in the — in the months ahead, and I want to thank the Red Cross and I want to thank America's blood banks for the work that they're doing to bring our donors in and to get this plasma.

For the — for the tens of thousands of people that have already donated plasma, thank you for what you've done. You are literally saving lives. And we need hundreds of thousands more to please come forward.

If you've been infected and recovered, please go to Coronavirus.gov and — or reach out to your American Red Cross outlet or your local blood bank, and please be a donor.

We now have more than 48,000 patients that have received convalescent plasma thanks to the work of American researchers and physicians, the FDA, HHS's Office of the Assistant Secretary for Preparedness and Response, and groups like the Red Cross and our blood banks.

This effort is just one piece of what the President is leading towards bringing therapeutics to the market. So we have remdesivir, we have steroids for lung injury, and now we bring convalescent plasma to people. We've invested more than \$1.7 billion through our Operation Warp Speed, which is the President's initiative to get vaccines, therapeutics, and diagnostics to the American people in record time.

And when it comes to therapeutics, warp speed means weeks, not months. Earlier this month, through Operation Warp Speed, we announced a \$450 million agreement with Regeneron to support their promising monoclonal antibody cocktail.

What makes OWS so bold is that we've now paid to begin making doses of this Regeneron product before it receives FDA authorization or approval. And that means that if, and only if, this drug meets FDA's gold standard for safety and effectiveness, we'll have tens of thousands or hundreds of thousands of doses to distribute to American patients right away, as soon as this fall.

And that's what today is about also: ensuring that even as the FDA reviews the data on convalescent plasma, we have plenty of supply, we have access for people. It also enables us to develop new therapies such as hyperimmune globulin, which is the distilled, purified version of our convalescent plasma.

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So thanks to everyone who's donated. And thank you, Mr. President, for this national call to action to donate. And thanks to all of our future donors. Thank you, Mr. President.

THE PRESIDENT: Thank you very much, Alex. Appreciate it.

Dr. Collins, please.

DR. COLLINS: Well, thank you, Mr. President. And good afternoon, everyone. It's wonderful to be in this beautiful space. And thanks very much, Gail, and everybody at Red Cross for hosting us here.

We try to make it clear what a remarkable gift Americans have been giving by donating plasma if they've recovered from COVID-19, because that has the potential to help lots of people.

Your own human body is a wonderful, little biotechnology factory, even if you might not think about it that way. Your immune system is ready to take on whatever kind of pathogen happens to wander into your environment and potentially threaten you. And we know this is a particularly impressive virus for what it can do. And yet, most of us, thank God, once exposed to this, do figure out how to recover from it because that immune system kicks into gear and makes those antibodies that then allow the virus to lose the battle and you to win.

And now, having done so, you're in a position to be able to donate your biotechnology product, which is your plasma, to somebody else who's just now getting sick with this disease, and you have a chance to help them if their own factory hasn't quite kicked in.

Americans are amazing, and the way in which people have been doing this is truly inspiring. Americans seem to believe that biblical verse, "To whom much has been given, much will be required." To whom coronavirus has been given and they've recovered, apparently they have recognized that they have something else that they can do to help the next person, and that is inspiring. And we're here to encourage more and more people to see that as something practical and important they can do at the time of this global pandemic.

You already heard, though, from — the comments made by the Secretary that this is part of a remarkable menu of therapeutics, of treatments that are being developed against coronavirus. And this particular one also opens the door to other kinds of immunetherapy.

The monoclonal antibodies that were mentioned, where money has now been devoted to scaling that up with a company called Regeneron, is basically to take the part of the convalescent plasma that we think is the most potent and figure out how to turn that into a purified product. We're not quite there to show yet whether that works, but that is also a very promising approach.

And there are a couple of trials of monoclonal antibodies from other companies that are on the launching pad starting as soon as tomorrow.

So all of this fits together with what the Trump administration has been doing, through Operation Warp Speed, to literally bring all hands on deck from the public sector, from the private sector. Nobody worrying too much about who's going to get the credit. Let's just move this forward and save lives. And all of the Americans who've been donating their plasma are a big part of that team.

So, thanks. It's wonderful to be part of this event this afternoon.

THE PRESIDENT: Thank you, Francis. Appreciate it very much.

Kate, please.

MS. FRY: Thank you, Mr. President, for having this important event today. America's Blood Centers is the national trade association for independent community blood centers.

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Our members are responsible for over 60 percent of the nation's blood supply and have been at the forefront of convalescent plasma collections in the U.S. over the past four months.

There are more than 60 independent community blood centers, as well as hospital blood banks, operating hundreds of donation facilities, taking part in the effort to collect convalescent plasma to ensure this product gets to every patient in every hospital across the country.

We're excited to announce that, today — that as of this week, independent community blood centers have distributed more than 100,000 doses of COVID-19 convalescent plasma to patients in need. Every blood center — small, medium, and large — across the country has mobilized to do their part in this effort. Of course, we are not slowing or stopping down in any kind of way; we are indeed mobilizing to do even more. And we are projecting that we will double our current number of doses by the end of August.

This unprecedented response by community blood centers demonstrates their commitment to meeting patient need wherever it is. America's Blood Centers and its members will continue to collaborate with the administration, federal agencies, and all stakeholder partners to ensure and advance the safe collection and distribution of convalescent plasma.

Now, the single most important thing to our ability to do more in distributing convalescent plasma is having donors. And so this event is so important in terms of our ability to educate the American public and encourage them to donate.

I would say that when you make a donation appointment — and appointments are critical here at your local blood center — you'll go through a process. The whole appointment takes about 90 minutes, and it's a safe and easy way to help your fellow Americans.

And so we are following — all blood centers are following social distancing protocols. They've implemented infection disease protocols as well. So this is a very safe and easy way to help others.

So thank you again for having this event, and we look forward to being part of this effort.

THE PRESIDENT: Thank you very much, Kate. Appreciate it.

Tony and Deborah, please.

DR. FAUCI: Thank you very much, Mr. President, for support of this very important program. When we talk about what is going on in this country and the challenge we're facing, we often say that it is something where we are all in it together, and we all have to pull together.

An important part of the process of being in it together and pulling together is helping each other. You know, and I can think of nothing more manifesting, the helping of each other, than someone donating from their experience of being ill. And this is something that I think is part of the American spirit, and we should be proud of it, and we should show it. So it's a very important thing. It's an important part of the entire response to this outbreak.

I want to mention that when we do something like give convalescent plasma, it's important to understand, as several of us have mentioned, that it is important part of the spectrum of interventions and response. We have good therapies and we'll get better therapies for people with advanced disease. We have the dexamethasone for people on ventilators, the remdesivir with people who are hospitalized, who have lung involvement.

And now we're talking about another important part of intervention — is the intervention early in infection to prevent people from needing to go to the hospital. And that's really what convalescent plasma is — because the mechanism of it, it is directed against the

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virus. It's taking the machinery that Francis has spoken about that the body makes to get a protein to block the virus. And that's exactly what this is all about.

Now, it's also important to point out that this could be a proof of concept, because when antibodies work, it tells you a few things: It'll tell you that when you have a vaccine and you induce antibodies, it could work.

And this is the good news that's juxtaposed to what happened a couple of days ago when we went into the phase three trial for a vaccine. Some of you may heard — may have heard me say that I was "cautiously optimistic" — a word that I use often — that we will be successful with a vaccine. One of the reasons is that, in the phase one study, the vaccine induced response that was comparable, if not better than what we see in convalescent plasma. So here's where the work of vaccine essentially merges with the work we're doing now with convalescent plasma.

So that's the reason why we think it's so important and why it's so important for people to donate.

Thank you, Mr. President.

THE PRESIDENT: Thank you very much, Tony. Thanks.

DR. BIRX: Thank you, Mr. President. And thank you for lending your voice to the day's important call to action and really making the two critical points of what we're calling every American to do. Thank you for noting how important it is for every American to give back by wearing a mask, by socially distancing, and from avoiding crowded places where they may not be able to social distance or wear a mask — and we know what we're talking about: parties and bars.

Thank you for also really calling to action for those who have recovered to donate lifesaving plasma to others. And I think these two pieces together — knitted together to stop the spread of the virus through masks, social distancing, and avoided crowded spaces — either indoors and outdoors — and protecting the vulnerable, and at the same time, calling for action to increase our therapeutic abilities to treat more patients.

Thank you.

THE PRESIDENT: Thank you very much. Please. Thank you.

MR. SCHECHTER: Mr. President, thank you for having us today, and thank you for this national call to action. We think it's very important.

At LabCorp, our employees have been working seven days a week, three shifts a day, to try to perform as many tests as fast as we possibly can to see who has the virus. I'm proud to say that today we can do 180,000 tests per day, and we can turn those tests around in one day for priority patients, and two to three days for all other patients.

And I want to thank Dr. Hahn, Admiral Giroir, Secretary Azar for all their help to ensure that we have what we need to get these tests turned around even faster, and we're going to continue to build capacity.

At the same time, we realize that there's more that LabCorp can do. And since the beginning, we were part of a coalition called the "Fight Is In Us." And it's a group of companies that came together to try to encourage people that have had the disease in the past, to give plasma.

To accelerate that, we're going to announce in the next several days that we will have free high-affinity antibody tests available for anybody through their physician, where if they're going in for routine bloodwork, the physician could just add on an antibody test; we will run it. And the only thing that we ask is that if the patient has antibodies, that they please consider to donate plasma.

THE PRESIDENT: It's a great idea. Thank you very much. Appreciate it.

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Dr. Hahn, please.

DR. HAHN: Thank you, Mr. President. Based upon your call to action, FDA has responded to remove any unnecessary barriers to the speeding of medical products during this pandemic.

I want to thank the American Red Cross, the American Blood Centers for the collaboration that we've had in the development of the convalescent plasma program.

As the President and Secretary Azar mentioned in March, FDA began working with our colleagues to develop this program. The Mayo Clinic has initiated what's called an expanded access program, which has really allowed physicians around the country to order convalescent plasma as an early treatment for patients. A number of clinical trials beyond the expanded access program are taking place.

We're encouraged by the data; we've seen that this is a safe treatment. And we're encouraged by the early promising data that we've seen. And as the President mentioned, we're studying these data to determine, ultimately, the safety and efficacy of this product.

In the meantime, we know that doctors are writing these orders, that patients who are hospitalized need this, and so the call to action to donate is so important. And even if, at the end of the day, convalescent plasma doesn't turn out to be the treatment we think it might be, remember that your donations still count with the American Blood Centers and the American Red Cross. They can truly save lives.

And just to put another point on the therapeutics development: FDA is now overseeing over 200 clinical trials of therapies that the great American biomedical research enterprises put forward, and more than 400 are in the planning stages.

So we have a tremendous pipeline of therapies for COVID-19. It's been an unbelievable private-and-public partnership. And, Mr. President, thank you for your leadership.

THE PRESIDENT: Stephen, could you give a few words on the speed with which we're getting the vaccines out and approved –hopefully approved and finalized — and where we are with phase one, two, and three, et cetera?

DR. HAHN: Yes, sir. We have a number of companies that have come forward with vaccine candidates. Some of those are in Operation Warp Speed. And I want to emphasize the fact that FDA has a very bright line drawn between its actions and Operation Warp Speed. We are the independent regulator. And as the President said, we'll ultimately be calling the balls and strikes with respect to the safety and efficacy of a vaccine.

We have six vaccine candidates that have come to FDA, and we've given them the "safe to proceed" into clinical trials. Two are currently in the latest phase of trials, called phase three; they started this week. Another one is planning to go into phase three in August. And then an additional three are in other phases of the clinical development.

Four additional vaccines have come to us, and we expect to allow them to go forward fairly soon. And then there are a number of 50-plus vaccines that have come in house for the pre-application process.

I think we can all agree that this has been sort of a remarkable effort from when the virus was first identified at the NIH, and the sequence was made, to the initiation of the first clinical trial — NIAID spending a lot of time getting that to that point. It really is record speed.

But also, at your direction, Mr. President, we aren't cutting corners with respect to the development, and we will not be cutting corners with respect to the assessment of the safety and efficacy of the vaccine.

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THE PRESIDENT: And you're literally many, many months and even years ahead of schedule in terms of approval. So we really appreciate the FDA. And please let us — let everyone know how we feel, all of us. Thank you. Great job.

Jerome, please.

SURGEON GENERAL ADAMS: Thank you, Mr. President. I really appreciate you being here today.

The theme of this national call to action is: "We're in this together." And when I think about all of us being in this together, I think about an iconic American image: Rosie the Riveter. Rosie the Riveter became a part of our history because we were at war. People were scared. People felt helpless. But the American spirit is all about people coming together — coming together to defeat a common enemy. And we have a common enemy now; it's COVID-19. But we also have tools that everyone can bring to bear to really help us overcome this enemy, and one of those is convalescent plasma.

One thing I want to add to the discussion that hasn't been brought up yet is that the average age of donation of blood and plasma is over the age of 60. So to the young people out there: We've got some work to do. The seniors are showing us up. We need everyone to do their part, because we're all in this together.

I also want to foot-stomp something that Dr. Birx mentioned and that Dr. Fauci mentioned. There's a spectrum that we have here of treatments that are way downstream, treatments that are midstream, and then preventative measures that we can all take, because we're all in this together.

And, Mr. President, I want to thank you for emphasizing the three W's: Number one, wash your hands. Number two, watch your distance. Number three, wear a mask.

I was in Miami just a few weeks ago and I promised them I would tell you this. I was in Trump country and they told me to deliver you a message, Mr. President. They told me to tell you, you look badass in a face mask. (Laughter.) I promised them I would tell you that. Miami, I told the President he looks badass in a face mask. (Laughter.)

We are all in this together. Give blood. Give plasma. Save a life. We'll get through this, America.

THE PRESIDENT: Thank you, Jerome, very much.

Please.

MR. PERREAULT: Thank you, Mr. President, for having me here today and, really, to join the partners that are here together to join our mission of combating this disease with our particular expertise and technologies.

I also want to thank you for your leadership. I think that no one has seen this in the world. It takes resolve and it takes effort, and you've shown that both with your leadership but also with the founding of Operation Warp Speed. So thank you for that.

I also want to thank you for your outstanding team that we're working with — great people; really have done a fantastic job — and for proactively engaging the private sector to combat COVID-19.

I am Paul Perreault. I'm the CEO of CSL Limited. Our legacy in fighting infectious disease goes back to 1901, with Emil von Behring, who was the first Nobel Prize winner in medicine, who actually utilized plasma as a means to fighting off diphtheria. So our history is long in this space.

Since then, CSL has been committed to innovating and developing therapies for rare and serious diseases. That's our business. We currently have several R&D programs that are fighting for COVID-19, including vaccines, monoclonal antibodies, and plasma therapies. We are one of the world's largest collectors of plasma.

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I'm here today representing all the manufacturers of hyperimmunes, including the COVID-19 Plasma Alliance, which is really an unprecedented partnership of world leading plasma companies who have joined together to help develop a plasma therapy to treat COVID-19.

And I have to say that the help from the FTC was important as well because we're typically competitors, and this is really a combination of all of these companies working together.

The plasma donated by people who have fought off COVID-19, as you've already heard, has precious antibodies — really important antibodies to fight off this disease. These antibodies can be isolated and then they can be converted into what we term a "hyperimmune plasma therapy" that, in theory, could be used to treat active COVID-19 infections. It builds on the concept of plasma transfusion. But the product is more like a standard medicine. This is an important approach and is well established in treating other infectious diseases like rabies or tetanus.

Working jointly with the NIH, the major plasma manufacturers have designed a clinical trial that will be enrolling individuals in the month of August. And if the data from this supports our hypothesis, we could be in a position to submit the hyperimmune therapy to Dr. Hahn for immune therapy against COVID-19, by the end of this year.

But we need plasma, and we need plasma donors. So we need them wherever they are. We need them to donate blood. We need them to donate plasma. And we also need plasma in general, because plasma is used to treat other rare diseases.

So this call to action, that we're in this together — the fight is in us. We have to work together. And this call to action to donate plasma and help us fight against COVID-19 is really an important step in making this happen.

So we thank you for bringing us together.

THE PRESIDENT: Thank you very much.

MR. PERREAULT: And thank you, Gail, for hosting us.

THE PRESIDENT: And I hope you'll be able to do it even before the end of the year and maybe substantially before that, from what I'm hearing.

Okay, thank you very much.

MR. PERREAULT: Thank you.

THE PRESIDENT: Would anybody have any questions of these very brilliant people having to do with plasma, antibodies? Any questions?

Steve, go ahead.

Q The death toll is now 150,000. What is the current projection going forward? What should we expect in the next couple of months?

THE PRESIDENT: Well I'd let — perhaps, Tony, do you want to discuss that, please?

DR. FAUCI: You know, many of the (inaudible) — look at it, we almost will not have enough that would be utilizable, particularly not only for the administration, but also for what was just mentioned about the supply of the hyperimmune globulin. So, really, an unlimited amount. There really is as many as we possibly can get — in the hundreds of thousands.

Q Are you going to recommend that Americans wear goggles, as well as face masks, to defend against the virus? Is that going to be one of the CDC's recommendations?

THE PRESIDENT: Well, I can tell you I only heard of goggles for the first time about one hour ago. Now I'm hearing about goggles. So I don't know.

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Deborah, do you want to discuss that?

DR. BIRX: So I believe Dr. Fauci talked about this yesterday. But we have, in the hospital systems and having — for exposure — have had people using face shields. And I think you've seen that through my tour through the United States and 14 states across the country where the President sent me to make sure that we were combating the virus well on the ground.

Tennessee has created teachers — special teacher packs to ensure that every teacher has a face mask — a face shield, gloves, and hand sanitizers. And I think we're trying to bring these best practices back to ensure that teachers feel safe in the classroom in the same way that doctors and nurses feel safe in the hospitals to decrease their exposure.

THE PRESIDENT: I think when you look at Miami, by the way, or Florida, in particular, it looks like things are getting much better. Arizona getting much better. Heading down. Heading in the right direction. Some other areas getting much better. Could be catching on, unfortunately, in a couple of areas. We don't know quite yet, but we'll be able to report that soon. But some very big progress being made in some of the states that two weeks ago looked like they were going to be quite bad. And some great progress made.

All right, any other questions? Please.

Q Tom Howell, Washington Times. Are you concerned at all about the lag time it takes to get a test back? We've heard reports of a week or more. The gentleman from LabCorp talked about that a little bit. What's — what's going on there? Has there been improvement?

THE PRESIDENT: So we're getting — mostly now, we're ordering as many of the immediate tests, which is 5 minutes to 15 minutes — even a little bit less, in some cases, than five minutes. But we're trying to get those tests. We have pretty close to 50 percent. I call them "short-term tests," but we're up to about 50 percent, which is amazing.

The other tests, while good, you have to send them, then they have to do the work, and they have to send them back. So the process takes long, just in terms of delivery. We really are liking the short-term test where you find out immediately whether or not you have a problem. And that's what we're striving for. But we're already up to approximately 50 percent. Is that correct, Deborah?

DR. BIRX: I think with the new antigen tests that are available now to nursing homes, that will really help our turnaround times — to get them out, more specifically. But you have charged us to get that turnaround time down across the board, and we're working with FDA to make pooling available.

The reason LabCorp has been able to decrease their turnaround time so remarkably is they moved to pooling several weeks ago. That's dramatically increasing our throughput throughout the country. And so we really need to call on all the laboratories to learn from LabCorp and others that are doing pooling, like the Broad and LabCorp, to really increase our turnaround times — to decrease our turnaround time. So we know that it's possible that we can decrease it by at least 50 percent, if all of our laboratories move to pooling.

So, sir, we're doing as you said, and we're going to decrease those turnaround times.

THE PRESIDENT: Good. Thank you.

And how is LabCorp doing about turnaround?

MR. SCHECHTER: Yes, so, right now, Mr. President, for priority patients — those in hospitals or those in nursing homes and hotspots — within one day, we can turn them around.

THE PRESIDENT: That's great.

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MR. SCHECHTER: For everybody else across the country, we turn those around in two to three days on average. And we can do 180,000 of those tests per day, and we're still increasing capacity.

And as Dr. Birx said, we're going to be doing pooling and multiple other things. So we will continue to work hard.

THE PRESIDENT: So then for nursing homes, one day, and something more than that for everyone else. But three days looks like it's a pretty good target.

MR. SCHECHTER: Yeah, well, on average, two to three days. So we shoot for two to three days. So if we can get it to two days on average, even better.

THE PRESIDENT: Well, that's really — you know — that's very good. We'd be happy with those numbers. And numbers that we are happy with, and we use a certain test around here that goes very quickly. And it's just been recently developed. So we've done an amazing job. Everybody at this table has done, really, an amazing job in coming up with testing, and testing that works.

Steve, go ahead.

Q One issue that has come up is, once you do have a vaccine, how do you properly distribute it? How do you get it out quickly to (inaudible)?

THE PRESIDENT: Well, when we have the vaccine, we have the military all lined up, and the military is going to be doing it in a very powerful manner. These are people that don't usually do vaccines. They do soldiers and they do lots of other things that, frankly, are more difficult. But we have our general, and logistically, he's all set.

Tony, do you want to say something about that?

Dr. FAUCI: That is correct. As the vaccine rolls out, we'll be getting them distributed. And as you probably have heard, we are going to make sure that we do it in an equitable way and it's representative of the populations who need it the most. And we have the standard way that we determine that, with the ACIP working with the CDC.

But Dr. Collins and Dr. Redfield have put together, with the National Academy of Medicine, a group that will fortify that decision-making process so that we're making sure that we're very fair and equitable in getting the vaccine distributed properly.

THE PRESIDENT: And I think I could have Francis say that tremendous progress has been made on the vaccine, beyond anything that we would have thought if you go back six months.

What do you think?

DR. COLLINS: It is just, frankly, quite astounding, Mr. President. I've been at NIH for 27 years and director for 11, and I've seen some amazing things happen. But the way in which the whole research community — public and private, philanthropies — everybody has come together to work on this, not worrying about who gets the credit, trying to figure out how to strip away anything that's going to slow things down.

And I think all of us motivated by the fact that this is the most serious problem we've encountered in our professional lifetimes, even a day matters. And so that's why a lot of people look kind of sleepy, because we're all working 24/7, trying to make sure that nothing possibly slows this process down.

Yeah, the vaccines — this week is a big week, as you just heard, having two phase-three trials started in the very same day, this past Monday. And based upon very impressive phase one data, showing that people who got that in the phase one trials, developed these high levels of neutralizing antibodies that should be very predictive of protection. But you don't know until you actually run the trial in those 30,000 people.

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By the way, you heard earlier about Coronavirus.gov, which is a place you can go to to find out how you can donate plasma. There's another thing you can do if you go to that website, which is to sign up to say you're interested in a vaccine trial. And we need people to volunteer for that as well, because we're going to — with these four or five trials coming along very quickly, each of which needs 30,000 volunteers — that's a lot of people. And we need them.

THE PRESIDENT: And, Francis, we're working very well with other countries.

DR. COLLINS: We are indeed. And science has always been international, and it certainly is right now. And we work with our colleagues in Europe and the UK and Asia in a way that I think represents the best of the best. And again, everybody recognizes we're all in this together across the whole planet.

THE PRESIDENT: Okay, thank you very much, everybody. Thank you. Thank you. Thank you.

END

3:40 P.M. EDT

7/30/2020: Hahn, S: Posts Public Service Announcement requesting COVID-19 Convalescent Plasma donations. US

FDA, July 30, 2020. https://youtu.be/PIX15rWdBbY

(as of 11-14-2020, <u>ONLY</u> 1,458 viewings of this PSA from 8/30/2020 to 11/14/2020!)

7/30/2020: McKend E: Dr. Birx: Plasma donations needed as coronavirus cases spike Nationwide. https://spectrumnews1.com/ky/lexington/health/2020/07/30/dr--birx--plasma-donations-needed-as-coronavirus-cases-spike-nationwide

8/2020: U.S. Department of Health and Human Services, Office of Civil Rights: Updated Guidance on HIPAA and

Contacting Former COVID-19 Patients about Plasma Donation August 2020. https://www.hhs.gov/sites/default/files/guidance-on-hipaa-and-contacting-former-covid-19-patients-about-plasma-donation.pdf

8/11/2020: https://www.rev.com/blog/transcripts/donald-trump-press-conference-transcript-august-11-kamala-harris-college-football-covid-19-vaccine

President Donald Trump: (07:45)

Operation Warp Speed is the largest and most advanced operation of its kind anywhere in the world and anywhere in history. We've treated more than 86,000 Americans with convalescent plasma. A recent Mayo Clinic study found that this treatment may produce results, which are incredible. We look to a reduction and reduce mortality rate by 50% and possibly even more than 50%. I urge Americans who have recovered from the virus to go to coronavirus.gov and sign up and donate. We would really appreciate that because it's been very successful, unbelievably successful, and we would love you to go and donate.

8/19/2020: https://www.rev.com/blog/transcripts/donald-trump-press-conference-transcript-august-19

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John: (15:30)

Mr. President, you have been very bullish on the promise of convalescent plasma to treat coronavirus. The FDA appeared to be on the brink of issuing an emergency use authorization for convalescent plasma. But after hearing from top officials at the NIH that there wasn't enough evidence to go ahead with that, the FDA has put that on pause. Your reaction to that. And do you believe that convalescent plasma should be in the arsenal of treatments-

Donald Trump: (15:57)

Well, I hear great things about it, John. That's all I can tell you. And it could be a political decision and-

Donald Trump: (16:02)

I can tell you and it could be a political decision because you have a lot of people over there that don't want to rush things because they want to do it after November 3rd, and you've heard that one before, but I've heard fantastic things about Convalescent Plasma, and I've heard numbers way over 50 percent success and people are dying and we should have it approved if it's good and I'm hearing its good. I heard from people at the FDA that it's good, so we'll see. I'm going to check that right after this conference.

8/23/2020: https://www.rev.com/blog/transcripts/donald-trump-august-23-white-house-covid-19-press-conference-transcript

Donald Trump: (04:47)

On the therapeutics front, this is what I've been looking to do for a long time. This is a great thing. Today, I'm pleased to make a truly historic announcement in our battle against the China virus that will save countless lives. The FDA has issued an Emergency Use Authorization, and a that's such a powerful term, Emergency Use Authorization, for a treatment known as convalescent plasma. This is a powerful therapy that transfuses very, very strong antibodies from the blood of recovered patients to help treat patients battling a current infection. It's had an incredible rate of success. Today's action will dramatically expand access to this treatment.

Donald Trump: (05:39)

I want to thank Dr. Hahn and Secretary Azar. I want to thank the FDA, all of the people that have been working very hard on this. It showed tremendous potential. It's only made possible because of Operation Warp Speed. That is everybody working together. We're years ahead of approvals that we would be if we went by the speed levels of past administration. We'd be two years, three years behind where we are today, and that includes on vaccines that you'll be hearing about very soon, very shortly.

Donald Trump: (06:16)

To deliver treatments and vaccine to save lives, we're removing unnecessary barriers and delays, not by cutting corners, but by marshaling the full power of the federal government. We provided \$48 million to fund the Mayo Clinic study that tested the efficacy of convalescent plasma for patients with the virus. Through this study over 100,000 Americans have already enrolled to receive this treatment, and it is proven to reduce mortality by 35%. It's a tremendous number. The FDA, MIT, Harvard, and Mount Sinai Hospital have also found convalescent plasma to be a very effective method of fighting this horrible disease. Based on the science and the data, the FDA has made the independent determination that the treatment is safe and very effective.

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Donald Trump: (07:12)

Recently, we provided up to \$270 million to the American Red Cross and America's blood centers to support the collection of up to 360,000 units of plasma. In late July, we launched a nationwide campaign to ask patients who have recovered, and these are patients that have been incredible the way they've donated. But these are people recovered from the virus to donate plasma. Since then, weekly plasma donations have doubled. Today, I once again urge all Americans who have recovered from the virus to go to coronavirus.gov and sign up and donate plasma today, please. It's been really an incredible ... Just incredible people. The country has united so strongly behind this.

Donald Trump: (08:08)

I'll go over the numbers, but if you look at what's happened and the success that we've had that people don't talk about, the United States has experienced the lowest case fatality rate of any major country in the world. You don't hear that. The European Union's case fatality rate is estimated to be three times higher than that in the United States. Europe has seen 33% more fatalities compared to a typical non-pandemic year than the United States.

Donald Trump: (08:38)

I just want to ask two of our people that have done such a fantastic job, Alex Azar and Stephen Hahn to say a few words. Stephen, I want to thank you because the FDA really stepped up and especially over the last few days in getting this done. The results have been incredible, and I think you'll see the results even go up very substantially. So we appreciate it. And maybe I'll ask Alex to go first, and then Stephen. Thank you very much, Alex.

Alex Azar: (09:06)

Well, thank you very much, Mr. President. Thanks for the bold leadership that allowed us to deliver this very happy news today. Thanks to your all-of-America approach, America has done more than any other country to expand the arsenal that we have to battle COVID-19. Thanks to early efforts by your administration, Americans have broader access to these treatments, including convalescent plasma, than patients anywhere else in the world.

Alex Azar: (09:33)

In early April, early in our fight against COVID-19, the FDA, BARDA, the Mayo Clinic, and other partners sprang into action to set up an expanded access protocol for this promising treatment. President Trump is the right-to-try President, and he's fought hard to ensure that Americans can have access to promising COVID-19 treatments. Convalescent plasma has been a tried-and-true therapeutic method in prior outbreaks, but the President wanted to ensure that we develop the data to support its use. This FDA authorization is one result of that effort.

Alex Azar: (10:06)

The data we gathered suggests that patients who were treated early in their disease course, within three days of being diagnosed with plasma containing high levels of antibodies, benefited the most from treatment. We saw about a 35% better survival in the patients who benefited most from the treatment, which were patients under 80, who were not on artificial respiration. I just want to emphasize this point because I don't want you to gloss over this number. We dream in drug development of something like a 35% mortality reduction. This is a major advance in the treatment of patients. This is a major advance.

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Alex Azar: (10:51)

Convalescent plasma is one new tool that we've added to our arsenal against COVID-19 alongside remdesivir, steroids, and a number of other promising options currently being studied. Because of the President's Operation Warp Speed, we expect to have other new results and new options reaching patients as soon as this fall. Operation Warp Speed is supporting experimental therapeutics all the way through to manufacturing, so that if they meet FDA's gold standard for safety and efficacy, they can begin reaching patients without a day wasted.

Alex Azar: (11:24)

Americans who have tested positive for and recovered from COVID-19 can go to coronavirus.gov to find out a quick, convenient way to play a potentially lifesaving role in our fight. Know if you donate plasma, you could save a life. We've also provided guidance, so healthcare providers can contact patients who have recovered from COVID-19 and give them information on how they can donate.

Alex Azar: (11:48)

So thank you again, Mr. President for supporting this remarkable progress against COVID-19, and I want to thank Dr. Hahn, Dr. Marks, and the entire team at the FDA for the speed with which they've approached this, the diligence to ensure that this meets the standards at FDA. I'll turn it over to Dr. Hahn, if it's okay, Mr. President.

8/23/2020: Dawsey J, McGinley L, Johnson CY, Kim SM: Trump to announce emergency authorization of convalescent plasma

as 'breakthrough' covid-19 treatment. The Washington Post.

https://www.msn.com/en-us/news/politics/trump-to-announce-emergency-authorization-of-convalescent-plasma-as-covid-19-treatment/ar-BB18hG1R

8/27/2020: https://www.rev.com/blog/transcripts/donald-trump-coronavirus-press-conference-transcript-july-27-talks-testing-and-vaccine-development

Donald Trump: (<u>00:57</u>)

The world is suffering from this China virus. Another dimension of Operation Warp Speed, is our focus on therapeutics to treat the virus over 100, including Remdesivir, which is having a tremendous impact. You see that with mortality rates and other things, statistically. Dexamethazone, convalescent plasma and antibody treatments, we have numerous treatments right now that are under study. I think over the next couple of weeks, we may actually have some very positive answers as to that. On July 7th, we announced a \$450 million agreement with Regeneron to begin advanced manufacturing of its antibody treatment, which is currently in late stage clinical trials, late stage. Due to the medical advances we've already achieved and our increased knowledge in how to treat the virus, the mortality rate for patients over the age of 18 is 85% lower than it was in April.

9/1/2020: https://www.rev.com/blog/transcripts/mike-pence-doug-ducey-dr-birx-press-conference-in-arizona-july-1

Vice President Mike Pence: (29:56)

Well, one of the ways the President marshaled a whole of America approach was we brought in all of the top pharmaceutical companies in America, which are the greatest in the world, early on in this pandemic. And we challenged them. We challenged them not only to develop vaccines, which are being developed and

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Table I: Transcript Excerpts and other pertinent references regarding COVID-19 Convalescent Plasma (CCP) in Chronological Order

researched at a record pace, but also the development of what are called therapeutics or to a lay person like me, it's the medicines that make you feel better. With the governor this week, we were able to inform him, and we'll receive another round of Remdesivir, we've been to acquire that from Gilead and distribute that to all 50 states. It's been having very positive effects on helping people recover from the coronavirus. The advent of a steroid treatment that has been utilized to good effect, helping people to recover. And of course, the convalescent plasma where people, over a million Americans have fully recovered from the coronavirus.

Vice President Mike Pence: (31:19)

And I would renew our ongoing request. Anyone in Arizona who's had the coronavirus, and fully recovered, contact your local Red Cross, donate blood so that you could be a part of providing that what's called convalescent plasma to people that we've also seen promising results. But on the subject of vaccines, I want to assure you the President initiated operation Warp Speed. And we put a team in place that's working now with the better part of a half a dozen very promising vaccine development. We remain hopeful that even before the end of this year, we'll have a vaccine available for the American people. But there'll be no compromising on the safety of a vaccine. We're going to go through the process, but the President's made it very clear that we're not going to wait to produce vaccines until we go through all of the different clinical trials that are typical.

8/26/2020 (Updated 9/3/2020): McDonald J: Trump, Hahn Mischaracterize Data on COVID-19 Convalescent Plasma. FactCheck.org https://www.factcheck.org/2020/08/trump-hahn-mischaracterize-data-on-covid-19-convalescent-plasma/

9/28/2020: https://www.whitehouse.gov/briefings-statements/remarks-president-trump-update-nations-coronavirus-testing-strategy/

The Vice President:

But you also challenged us and you challenged American industry to bring the full power and innovation of the American economy to bear on this moment. And whether it be PPE, where we forged a partnership to see to the delivery and the manufacture of hundreds of millions of personal protective equipment; whether it be how we started with 15,000 ventilators in the Strategic National Stockpile — and today, in partnership with GE Healthcare, Ford, and General Motors, we have over 150,000 ventilators in the Strategic National Stockpile; whether it be the extraordinary progress on therapeutics — remdesivir, convalescent plasma — that are literally saving lives; or whether it be, as you reflected, Mr. President, on our steady progress toward achieving a safe and effective vaccine before the end of this year, it's been that public-private partnership that you've led that's made these advances possible.

9/28/2020: https://www.rev.com/blog/transcripts/donald-trump-speech-transcript-on-covid-19-testing-trump-announces-plan-for-150-million-rapid-coronavirus-tests

Mike Pence: (15:38)

Mr. President, today's announcement is really emblematic of the public private partnership that you from the early days of this pandemic. As you said, we met today with the nation's governors. The White House Coronavirus Task Force completed our 38th conference call with America's governors. But all along the way from our very first meeting, you made it clear that we'd spare no expense to the federal government, the full resources of the federal government you made available to put the health of America first. But you also challenged us and you challenged

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Table I: Transcript Excerpts and other pertinent references regarding COVID-19 Convalescent Plasma (CCP) in Chronological Order

American industry to bring the full power and innovation of the American economy to bear on this moment. And whether it be a PPE, where we forged a partnership to see to the delivery and the manufacturer of hundreds of millions of personal protective equipment. Whether it be how we started with 15,000 ventilators in the strategic national stockpile, and today in partnership with GE Healthcare, Ford, and General Motors, we have over 150,000 ventilators in the strategic national stockpile. Whether it be the extraordinary progress on therapeutics, Remdesivir, convalescent plasma, that are literally saving lives.

10/02/2020: McEnany K twitter account: Letter from Sean P. Conley, DO, FACEP stating: Following PCR-confirmation of the

President's diagnosis, as a precautionary measure he received a single 8 gram dose of Regeneron's polyclonal antibody cocktail. He completed the infusion without incident.

https://twitter.com/PressSec/status/1312122950133272576?ref_src=twsrc_%5Etfw%7Ctwcamp%5Etweetembed%7Ctwterm%5E1312122950133272576%7Ctwgr%5E&ref_url=https%3A%2F%2Fwww.miamiherald.com%2Fnews%2Fnation-world%2Fnational%2Farticle246182890.html

10/3/2020: Agence France-Presse: Here's what we know about the antibody treatment Trump is getting for COVID-19. ScienceAlert. https://www.sciencealert.com/here-s-what-we-know-about-the-antibody-treatments-trump-is-getting-for-covid-19

The US biotech firm is concurrently running late-stage trials for hospitalized COVID-19 patients and for the drug's potential use as a prophylactic.

Antibodies are infection-fighting proteins made by the immune system that can bind to particular structures on the surfaces of pathogens and prevent them from invading cells.

Vaccines work by teaching the body to make its own antibodies, while scientists are also testing ready-made antibodies from the blood of recovered patients, called convalescent plasma.

But it is not possible to make convalescent plasma a mass treatment.

Researchers can also comb through the antibodies produced by recovered patients and select the most effective out of thousands, and then manufacture them at scale.

Regeneron's experimental COVID-19 drug, called REGN-COV2, is a combination of two antibodies, referred to as a "cocktail."

10/22/2020: U.S. Food and Drug Administration: Donate COVID-19 Plasma. Content current as of: 10/22/2020. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma; A PSA regarding Donating COVID-19 Plasma by Stephen Hahn, M.D., Commissioner, US FDA, July 30, 2020. https://youtu.be/PIX15rWdBbY (as of 11-14-2020, ONLY 1,458 viewings of this PSA)

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50.0 433 Table ii Availability of Passive Immunization 11-15-2020 copy.pdf

Table II-- Available Sources of COVID-19 Neutralizing Antibodies

Commercial Source **COVID-19 Convalescent** Eli Lilly: Bamlanivimab Regeneron: REGN-COV2 Plasma: (CCP). [2-6] [7-9] AABB and other FDA approved blood collection sites [1] Polyclonal Cocktail of two Antibody Type Monoclonal Antibody monoclonal antibodies Antibody Source human plasma by blood from human convalescent from human convalescent donation or plasmapharesis B-cells B-cells Best Effective Time for ASAP after documented ASAP after documented ASAP after documented administration COVID-19 positivity COVID-19 positivity COVID-19 positivity Type of FDA authorization 1. 4/3/2020 to present: FDA 1. Compassionate use: 1. Compassionate use: directed Expanded Access e.g.: Christopher Christie, e.g.: Donald Trump, (discontinued 8/23/2020) former governor of New President of the United IND clinical trials, individual Jersey. [15] States [17] eIND's [10-12] 2. 11/09/2020: FDA 2. FDA authorization 2. 8/23/2020: FDA Emergency Use pending. Emergency Use authorization authorization (EUA) for 3. Independent committee (EUA) for in hospital use outpatient use only in recommends discontinuing only [13] minimal-moderate enrollment in studies that 3. 9/2/2020: FDA symptomatology patients include patient with increased respiratory care withdraws/overwrites [16] previous Eligibility Criteria and continues only outpatient enrollment. [9] from documentation [14] FDA guidelines 1. 4/3/2020-9/2/2020: 11/9/2020: To treat only 1. EUA note yet approved --A. Expanded Access: in the outpatient setting by FDA Administration of CCP only mild to moderate affected in inpatients with SARS cases. Not authorized for symptomatology requiring any person who has an increased respiratory care and increased need for oxygen ICU care as per FDA [16] Eligibility Criteria guidelines. [11,12] --B. IND per trial protocol [11,12]--C. eIND -- FDA recommended using criteria of Expanded Access. [11,12]2. After 8/23/2020, Hospitalized patients only [13]. 3. 9/2/2020 overwrites recommendations and removes all Eligibility Criteria [14] **EUA** 8/23/2020 [13,19] November 9, 2020 EUA not yet approved

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	COVID-19 Convalescent Plasma: (CCP). [1]	Eli Lilly: Bamlanivimab [2-6]	Regeneron: REGN-COV2 [7-9]
EUA guidelines	1. Hospitalized patients only [13]	 Outpatient only. Only mild to moderate COVID-19 positive patients [4] 	No EUA
	Cost of FFP (\$409.62 for two 200 ml doses) [18] plus COVID-19 testing and Ab testing for high dose (HD) v low dose (LD)	\$375,000,000/300,000 = \$1,250 purchase price by the US government	estimates ~\$3,000 a dose [20]
Source	2 doses from one donor convalescent blood unit at least 14 days after COVID-19 infecton ~2 hour duration donation every one to three monthsorby plasmapharesis (apheresis) every two to three days	9 day USA supply possible	10 day USA supply possible
Availability	Limited only by availability of HD plasma donations at >5000 AABB blood banks and other donation sites [21]	possibly 300,000 and additional 650,000 by December 31, 2020	possibly 1.6 million doses once EUA approved
Possible total patients treatment by December 31, 2020	Limited by blood donation or plasmapheresis by COVID- 19 recovered patients (higher the dose of neutralizing antibodies the better	950,000	1.6 million

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- 2. Lilly: Lilly's neutralizing antibody bamlanivimab (LY-CoV55) receives FDA emergency use authorization for the treatment of recently diagnosed COVID-19, November 9, 2020. https://investor.lilly.com/node/43931/pdf
- 3. Lee SM: The FDA has authorized the COVID-19 antibody drug that Chris Christie took. BuzzFeed News, November 9, 2020. https://www.buzzfeednews.com/article/stephaniemlee/fda-coronavirus-antibody-therapy-eli-lilly

- 4. Hinton DM, RADM, RN, MS, FDA Chief Scientist to Robert P. Kadlec, MD, MTM&H, MS, Assistant Secretary for Preparedness and Response, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, U.S. Department of Health and Human Services. EUA: Bamlanivimab, November 9, 2020. https://www.fda.gov/media/143602/download
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- 9. Regeneron: REGN-COV2 independent data monitoring committee recommends holding enrollment in hospitalized patients with high oxygen requirements and continuing enrollment in patients with low or no oxygen requirements, October 30, 2020. https://investor.regeneron.com/node/24461/pdf
- 10. Mayo Clinic: National Expanded Access Treatment Protocol. https://web.archive.org/web/20200404213000/https://www.uscovidplasma.org/ (From April 4, 2020), While the nominal title of "National Expanded Access Treatment Protocol" implies that the USA government was directing the process—IT WAS NOT! In fact, the hyperlink: onext to the National Expanded Access Treatment Protocol on the April 8, 2020 website version of Recommendations for Investigational COVID-19 Convalescent Plasma is representative of the FDA Disclaimer website disavowing any FDA responsibility regarding the National Expanded Access Treatment Protocol and misrepresenting itself:

Responding to the unprecedented challenge fighting coronavirus disease 2019 (COVID-19), the U.S. Government is supporting a national Expanded Treatment Protocol to collect and provide convalescent plasma to patients in need across the country. Plasma from recovered COVID-19 patients contains antibodies that may help fight the disease.

Working collaboratively with industry, academic, and government partners, Mayo Clinic will serve as the lead institution for the program, registering participating providers and potential patients who may benefit and qualify for this investigational treatment.

Subsequent iterations of the National Expanded Access Treatment Protocol: https://web.archive.org/web/20200407105003/https://www.uscovidplasma.org/ (From October 26, 2020).

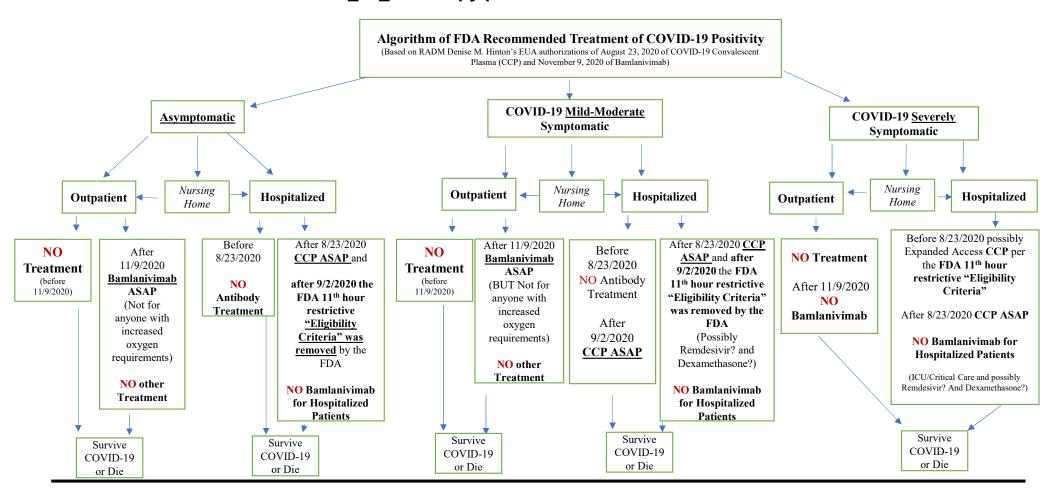
- 11. U.S. Food & Drug Administration: Recommendations for Investigational COVID-19 Convalescent Plasma. Content current 04/08/2020. https://web.archive.org/web/20200408215026/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
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- 13. Hinton DM, RADM, RN, MS, FDA Chief Scientist to Robert P. Kadlec, MD, MTM&H, MS, Assistant Secretary for Preparedness and Response, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, U.S. Department of Health and Human Services. EUA: COVID-19 Convalescent Plasma, August 23, 2020 https://www.fda.gov/media/141477/download
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https://newsnetwork.mayoclinic.org/discussion/expanded-access-program-for-convalescent-plasma-discontinues-enrollment-as-fda-authorizes-its-emergency-use/

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- 21. U.S. Food & Drug Administration: Donate COVID-19 Plasma. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma which contains the Public Service Announcement by Commissioner Stephen Hahn, M.D. which was published on-line on Jul 30, 2020 has been accessed by 1,464 people around the world over the last 108 days at https://youtu.be/PIX15rWdBbY.

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51.0 434 FDA recommendation 11_14_2020 copy.pdf



Alternate Appropriate Treatment of COVID-19 Positivity Algorithm (contrary to the FDA algorithm above):

COVID-19 Convalescent Plasma (CCP) or Monoclonal Antibodies ASAP after confirmation of COVID-19 positivity to All

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323 Table II – Mayo Clinic study morbidity and odds of dying copy.pdf

Appendix C – Copy of letters sent to 537 Congressional offices August 2020

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02 Dear Members of the US House of Representatives 8 28 2020

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Appendix G—NIH and FDA responses including establish NIAID Case #12276 6-10-2020 NIH and FDA responses including 6-6-2020 re NIAID Case #12276.pdf

Timeline Bibliography 2021-06-04 Master References

53.0 505.1 Remdesivir VA corr from Nov 2020 to 12_24_22020cpdf266

Andrus, Charles H. (STL)

From: Andrus, Charles H. (STL)

Sent: Thursday, December 24, 2020 2:06 PM

To: nejmgroup@mms.org; erubin@hsph.harvard.edu; mhamel@bidmc.harvard.edu;

lbaden@partners.org

Cc: Compton, Leslie R. (STL); McDonald, Jay R. (STL); George, Sarah L. (STL); Zacher,

Jennifer L. (PBM); candrus600@aol.com; charles.andrus@health.slu.edu; Stone, Richard

A., MD; Matthews, Kameron; Echevarria, Kelly; uscovidplasma@mayo.edu;

joyner.michael@mayo.edu; arturo.casadevall@einstein.yu.edu; Lieberman, Steven;

Clancy, Carolyn; jdrazen@nejm.org

Subject: FW: Remdesivir

Attachments: 01 12_20_2020 response to the USH.docx; 11 Time Crucial Independent Variable in

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December 24, 2020

Re: This is a cover letter (e-mail) regarding my Letter to the Editors of *The New England Journal of Medicine* regarding: Simonovich VA, Burgos Pratx LD, Scibona P, et.al.: A Randomized Trial of Convalescent Plasma in Covid-19 severe pneumonia, November 24, 2020. (email attachment item: "41 Letter to editor 12_13_2020 Not yet sent 12-20-2020.docx)

Dear NEJM editors:

On Saturday, June 19, 2004 at 6:55 PM, Dr. Drazen sent an e-mail of me to Dr. Catherine D. DeAngelis, Editor-in-Chief, *JAMA*:

Cathy,

I have a very large folder of electrons from this man.

J

Jeffrey M. Drazen, M.D.

Editor-in-Chief, New England Journal of Medicine Professor of Medicine, Harvard Medical School

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In my advocacy for the individual American veteran patient with regards to promoting the prohibition forever-goingforward of ghost surgery in the operating rooms of the VA (unsupervised surgery residents performing operations), I had clashed with American Academic Medicine and the Federal Government who had condoned Attending Surgeon absenteeism in the VA operating rooms (OR) since 1946 in the University-affiliated Veterans Affairs (VA) hospitals across America.¹⁻⁹ At the same time under Medicare auspices, the U.S. Departments of Health and Human Services (DHHS) and Justice (DOJ) through PATH (Physicians at Teaching Hospital) audits ¹⁰ in applying Intermediary Letter 372^{11,12} (IL-372: Medicare Rules for Resident Supervision by Attending Teaching Surgeons) audited the teaching hospitals of America between 1996 and 2006 and exacted a published amount of a quarter of a billion dollars in fines and penalties for fraudulent billing by Attending Surgeons of the Teaching Hospitals of the United States for violations of IL-372. As Congress had never approved subvention for the U.S. Department of Veterans Affairs (DVA) so as to allow the DVA to bill DHHS through Medicare for services rendered by the VA on Medicare eligible patients, IL-372 did not apply. The simple phrase in VHA Handbook¹³ 1400.1 of 2001: "Level 3: The Attending Surgeon is immediately available..." had been interpreted by some for a half century as the possibility that Attending Surgeons could stay at home or be in their private offices while the Surgery residents operated on a Veteran patient in a VA OR. The VHA removed any future possibility of outside-the-VA OR Attending Surgeon supervision for elective cases with the stated lowest level of resident supervision in the VHA Handbook¹⁴ 1400.01 completed in 2012: "Level D: Attending in OR Suite, Immediately Available."

Consistent with my litany¹⁻⁹ of submissions two decades ago that cluttered a very large folder full of electrons of *The* New England Journal of Medicine (NEJM) and my experience of following a paper-trail as a physician and surgeon of the Veterans Health Administration of the U.S. Department of Veterans Affairs of over 23 years, I submit all that is attached to this e-mail correspondence including my formal Letter to the NEJM editors responding to the NEJM original research article15 of November 24, 2020: Simonovich VA, Burgos Pratx LD, Scibona P, et.al.: A Randomized Trial of Convalescent Plasma in Covid-19 severe pneumonia, (e-mail attachment item: "41 Letter to editor 12_13_2020 Not yet sent 12-20-2020.docx) pleading with United States Medicine to advocate for the initiation of a Federally-organized, U.S. Food & Drug Administration (FDA) administrated collection of COVID-19 Convalescent Plasma (CCP) through the blood banks of America (e.g. The American Red Cross, etc.) with early administration (within the first 72 hours) to every person who becomes COVID-19 positive. As has been done for over a century, the Nobel-prize-winning concept of Passive *Immunization*^{16,17} has been used successfully as the early first-line empiric treatment in some diseases in which no other treatment was available (e.g.: the exception is dengue fever due to ADE—antibody-dependent enhancement). While it was impossible to use data from the Mayo Clinic's National Expanded Access Treatment Protocol¹⁸ for completion of any Phase I (safety)¹⁹ clinical trial as the project was "compassionate use" only²⁰, the "safety updates" from the Mayo Clinic of Dr. Joyner, Dr. Casadevall, et. al. successfully demonstrated that the administration of COVID-19 convalescent plasma in 20,000 patients is as safe as the readily available blood component of fresh frozen plasma (FFP) through the American blood banks.²¹

For the last century in every medical school in the nation, *Passive Immunization* has been a foundational teaching—So why has organized medicine and the United States government discarded it to the medical historical scrapheap? As physicians, don't we believe in that which we were taught in medical school? The formal Letter to the Editor of *The New England Journal of Medicine* regarding Dr. Simonovich's article¹⁵ of November 24th points out that the administration of CCP in this reported study was at **the wrong time (late)**--not during the early COVID-19 viremia when it should be administered--but in the late-stages in patients with severe pneumonia / MSOF when the body's immunologic response to the coronavirus disease is the negative overwhelmingly impediment to the individual patient's survival. Also attached to this e-mail is a how publicly CCP has been discussed over the last nine months. I have previously submitted much of my correspondence to the U.S. Copyright Office for historical preservation.²²⁻²⁴ Some of my correspondence with Dr. Fauci, Dr. Hahn, and the President over the course of the last nine months advocating for the use of CCP is included. I plead that you read the attachments.

At present, early empiric treatment with COVID-19 Convalescent Plasma seems destined for the medical historical scrapheap based on the late-in-the-disease administration of CCP as was done in the November 24th NEJM article. While during this holiday season many will view the movie *It's a Wonderful Life*²⁵, Frank Capra's Mr. Smith goes to

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Washington²⁶ is most apropos today with regards to the **Passive Immunization** in the early empiric treatment of COVID-19 Convalescent Plasma as it seemingly has become a lost cause:

Senator Jefferson Smith (Jimmy Stewart's character) on the Senate floor:

I guess this is just another lost cause, Mr. Paine. All you people don't know about lost causes. Mr. Paine does. He said once they were the only causes worth fighting for, and he fought for them once, for the only reason that any man ever fights for them. Because of just one plain, simple rule, "Love thy neighbor," and in this world today, full of hatred, a man who knows that rule has a great trust. You knew that rule, Mr. Paine, and I loved you for it, just as my father did. And you know that you fight for the lost causes harder than for any others. Yes, you'd even die for them, like a man we both know, Mr. Paine. You think I'm licked. You all think I'm licked. Well, I'm not licked and I'm going to stay right here and fight for this lost cause even if this room gets filled with lies like these, and the Taylors and all their armies come marching into this place. Somebody'll listen to me—some—

In the USA public eye, *Passive Immunization* has been a debated inconsequential concept for the last nine months in our struggle with the COVID-19 epidemic. A large portion of the U.S. Medical Community doesn't remember from medical school what *Passive Immunization* is even though it is applied successfully in the early empiric treatment (<72 hours) of many other disorders throughout the country daily—in the treatment of snake bites, rabies, tetanus in unvaccinated individuals, transplant patients and children with Kawasaki's disease, and postpartum Rh negative mothers. 17,27-29 While Research Immunology should complement Clinical Immunology, at present it seems to be in competition or conflict. We seem surprised with the increased "reactogenicity" observed with the second dose of the COVID-19 vaccine in the virus-naïve patient and with the first and second doses of the vaccine in COVID-19 convalescent patients—when every pediatrician over the last half century has warned mothers that after a "booster" vaccine their child might be fussy and febrile for the next 24 – 48 hours. Research Immunology and the application of early empiric treatment of COVID-19 with *Passive Immunization* appear to be publicly contradictory at present. (COVID-19 Convalescent Plasma could be readily available through the American blood banks if an organized national blood drive was established by the President of the United States). During this COVID-19 epidemic, we have also confused and equated "safety" (Phase I Trial) and "efficacy" (Phase II or III Trials) in our present COVID-19 clinical treatment trials 19 which has enhanced the confusion of clinicians over the application of early empiric Passive Immunization. Would we ever contemplate withholding from (1) an exposed immune-naïve patient a rabies vaccine³¹ after a dog bite by a rabid canine or (2) withhold tetanus hyperimmune globulin³² in the presence of a tetanus-prone puncture in a never-beforevaccinated patient demanding participation in Phase II or Phase III clinical trials with a placebo group to prove "efficacy"?³³—no Institutional Review Board would ever permit it.³⁴ With *Passive Immunization* versus a placebo control group, how can we offer a 50-50 chance of CCP versus FFP when this potential biosimilar³⁵ treatment (CCP) is labelled "investigational" and no other treatment exists in the face of the potentially fatal COVID-19 outcome—that is unethical.³⁸ Why have we rejected *Passive Immunization* as an early (< 72 hours) empiric treatment for newly-positive COVID-19 individuals?

As is stated in the first paragraph of the Executive Summary of the NIH COVID-19 Treatment Guidelines Panel³⁹:

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

Administration of *Passive Immunization* (e.g.: COVID-19 Convalescent Plasma, monoclonal antibodies, etc.) and an *Antiviral Drug* (i.e.: Velkury⁴⁰ NDA #214787 [Remdesivir]) <u>as soon as a person tests COVID-19 positive regardless of the severity of illness</u> should be the **Standard <u>Treatment</u> of Care of COVID-19 positivity** throughout the United States of America today.

Respectfully,

Charles Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine

Staff Surgeon, St. Louis (John Cochran) VAMC VA desk phone: 314-652-4100 ext. 54463

Home phone: 314-455-9482

Beeper: 314-491-2417

Please note, as with the attachments to this e-mail, I will submit this information to the U.S. Copyright Office to preserve the chronology for history.

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Responding to the unprecedented challenge fighting coronavirus disease 2019 (COVID-19), the U.S. Government is supporting a national Expanded Treatment Protocol to collect and provide convalescent plasma to patients in need across the country. Plasma from recovered COVID-19 patients contains antibodies that may help fight the disease.

Working collaboratively with industry, academic, and government partners, Mayo Clinic will serve as the lead institution for the program, registering participating providers and potential patients who may benefit and qualify for this investigational treatment.

Subsequent iterations of the National Expanded Access Treatment Protocol: https://web.archive.org/web/20200407105003/https://www.uscovidplasma.org/ (From April 7, 2020) https://www.uscovidplasma.org/ (From December 14, 2020).

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Serious Adverse Events. Key serious adverse events (SAE) related to the transfusion of convalescent plasma are reported in Table 2. Our report is not a comprehensive summary of all risks associated with hospitalization of COVID-19 but did assume that convalescent plasma potentially could cause life-threatening cardiac events and thrombotic events, so these were collected with an underlying assumption of attribution. Within four hours of completion of the COVID-19 convalescent plasma transfusion, 146 SAEs classified as transfusion reactions were reported (<1% of all transfusions). Of these SAEs, there were 83 non-mortality events reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction. Of the SAEs reported within four hours of plasma transfusion, there were 63 mortalities (0.3% of all transfusions) and 13 of these mortalities were judged as related (possibly, n=12; probably, n=1; definitely, n=0) to the transfusion of COVID-19 convalescent plasma. Within seven days of completion of the COVID-19 convalescent plasma transfusion, 1,136 other SAEs were reported. Of these SAEs, 87 thromboembolic or thrombotic events were reported, 406 sustained hypotensive events requiring intravenous pressor support were reported, and 643 patients suffered a cardiac event. Notably, the vast majority of the thromboembolic or thrombotic complications (n=55) and cardiac events (n=569) were judged to be unrelated to the plasma transfusion.

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Submission 09-12-2023 of BOOK1 Dear Mr. President -- COVID-19 and Where we went WRONG

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54.0 510 12_20_2020 response to the VHA USH.pdf

From: Andrus, Charles H. (STL)

Sent: Sunday, December 20, 2020 6:34 PM

To: Andrus, Charles H. (STL) < Charles. Andrus@va.gov>

Cc: candrus600@aol.com **Subject:** FW: Remdesivir

From: Andrus, Charles H. (STL)

Sent: Sunday, December 20, 2020 6:19 PM

To: Matthews, Kameron <Kameron.Matthews@va.gov>; Stone, Richard A., MD <Richard.Stone2@va.gov>; Echevarria,

Kelly <Kelly.Echevarria@va.gov>

Cc: Compton, Leslie R. (STL) < Leslie.Compton@va.gov >; McDonald, Jay R. (STL) < Jay.McDonald1@va.gov >; George, Sarah

L. (STL) <<u>Sarah.George@va.gov</u>>; Zacher, Jennifer L. (PBM) <<u>Jennifer.Zacher@va.gov</u>>; <u>candrus600@aol.com</u>;

charles.andrus@health.slu.edu

Subject: RE: Remdesivir

December 20, 2020

Richard A. Stone, M.D.

Executive in Charge, Veterans Health Administration (VHA)

("Authority to Perform the functions and duties of the Under Secretary for Health"

https://www.va.gov/opa/bios/bio_stone.asp_)

Dear Dr. Stone:

I thank you so much for participating and taking interest in my submissions to you last week regarding Remdesivir. I also appreciate the response that has been provided to me and you by Dr. Matthews at your request. Unfortunately, what has occurred has been based on a series of misadventures that were initiated in March 2020 by the U.S. Food and Drug Administration (FDA), the National Institutes for Health (NIH), the President's Coronavirus Taskforce, etc. that have led to confusion in treating COVID-19.

Included in Dr. Echevarria's initial response e-mail to me was a hyperlink to the National Institutes of Health COVID-19 Guidelines Panel's Treatment Guidelines. The first paragraph of the *Executive Summary* nicely outlines the pathophysiology of COVID-19 with an initial viremia and the subsequent COVID-19 positive patient's development of an out-of-control immunologic response resulting in pneumonia, SARS, and possibly multisystem organ failure:

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome cononavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

In March 2020, the FDA and in the Presidential Coronavirus Taskforce was presented with a dilemma: they knew that for 120 years one of the methodologies utilized in the treatment of any new (novel) virus was the noble-prize winning concept of **Passive Immunization** but the USA had few COVID-19-recovered convalescent patients to provide plasma which is the frontline agent in the administration of **Passive Immunization**. **Passive Immunization** is the use of immunoglobulins (that is neutralizing antibodies) as a temporizing immunologic treatment as antibodies attach to the antigens of the virus particle thus inhibiting some of the effects of the virus on the infected patient. **Passive**

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Immunization has been used successfully over the years with regards to Rabies and other infectious diseases and as antivenoms against snakebites, etc. The most successful example of **Passive Immunization** is RhoGAM: Providing postpartum mothers who are Rh negative within 72 hours of delivery of a Rh-positive baby with antibodies to neutralize and lyse fetal RBCs acquired by the mother during delivery. Approved by the FDA in 1968, RhoGAM has essentially made *hydrops fetalis* a disease of history in the USA. The other therapeutic agent mentioned in the NIH *Executive Summary* was the development of an antiviral agent effective against the coronavirus (e.g.: Remdesivir).

In March 2020, the first misadventure that occurred was the FDA's failure to declare COVID-19 convalescent plasma a biosimilar biologic. COVID-19 Convalescent Plasma (CCP) is nothing more than fresh frozen plasma (FFP), which is available from every Blood Bank, that specifically has been obtained from a patient that has recovered from the disease. As a general surgeon over the years, I have used countless FFP units in the resuscitation of patients with bleeding diatheses or exsanguinating from penetrating trauma, motor vehicle accidents, etc. FFP is fresh frozen (< -30° C) plasma--the serum component of every unit of blood. As such, the FDA, not the NIH or any other branch of the Federal Government has the sole statutory authority and responsibility for every blood component and every aspect of every Blood Bank in the USA, blood collection techniques, blood processing and assaying techniques, and blood administration in the United States. As such, the mechanism for collection, processing and distribution of COVID-19 Convalescent Plasma has been and is already in place under the statory auspices of the U.S. Food and Drug Administration (FDA).

Unfortunately, COVID-19 Convalescent Plasma (CCP) was deemed by the FDA *Investigational*. Anytime a drug or biologic is deemed *Investigational* by the FDA, a formal Clinical Trials process is initiated (see NIH https://www.clinicaltrials.gov/) mandating Phase 1 (a safety trial) and subsequently Phase 2 and 3 (efficacy trials) in the evaluation of a new drug or biologic. Therefore, the FDA established its *inclusion criteria* for Phase 1 clinical trials [safety only] and publicly announced the criteria in all its documentation on April 8, 2020, as in: Recommendations for Investigational COVID-19 Convalescent Plasma

(https://web.archive.org/web/20200408215026/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma):

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the <u>National Expanded Access</u> Treatment Protocol . These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - o Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

Normally, Phase 1 Clinical Trials according to the FDA should include 12 to 20 individuals. In a rush to provide easy access to CCP, the FDA announced in early April 2020 a collaboration with the Mayo Clinic in the National Expanded Access Treatment Protocol without the FDA assuming any responsibility as the little box with the arrow is the FDAs hyperlink to the FDA external disclaimer website. Unfortunately, under the Mayo Clinic COVID-19 Convalescent Plasma protocol website almost 95,000 units of CCP have been **safely** administered which could not be used as data for declaring a "Completed Phase 1 trial" due to its designation as under *Expanded Access*. *Expanded Access* =

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Compassionate Use precludes any research entity to use data from any compassionate use protocol. All clinical research in the USA is scrutinized by Investigational Research Boards (IRBs), and all IRBs are exclusively overseen and regulated by the FDA. Thus, the FDA could not declare CCP safe by a "Completed Phase 1 trial." Why is this so important? – because the only stipulation for the implementation of the Federal Law enacted by Congress and signed into law by the President of the United States in 2018, The Right to Try Act of (PL-115-176) is that a "Completed Phase 1 trial" be acknowledged. In essence, agencies of the U.S. Department of Health and Human Services have violated the intent of Federal Law by circumventing a "Completed Phase 1 Trial" with the present disastrous results.

The EUA for Remdesivir was first authorized by Rear Admiral Hinton, FDA Chief Scientist, on May 1, 2020 with similar strict *Inclusion* eligibility criteria as was applied to CCP.

https://web.archive.org/web/20200501204823/https://www.fda.gov/media/137564/download. The history of this rescinding of the severity criteria regarding Remdesivir on August 28, 2020 was reported in Rear Admiral Hinton's EUA update of October 22, 2020 https://www.fda.gov/media/137564/download which coincided on the same day of the FDA issuing a New Drug Authorization (NDA 214787) for Remdesivir by John J. Farley, MD, MPH, Director, Office of Infectious Diseases, Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda docs/appletter/2020/2147870rig1s000ltr.pdf
Without any physiology restrictions except for hospitalization, the FDA stated:

NDA 214787

NDA APPROVAL

Gilead Sciences, Inc. Attention: Ashley Rhoades, MBS, RAC Manager, Regulatory Affairs 333 Lakeside Drive Foster City, CA 94404

Dear Ms. Rhoades:

Please refer to your new drug application (NDA) dated and received August 7, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VEKLURY (remdesivir) injection, 5 mg/mL; VEKLURY (remdesivir) for injection, 100 mg/vial.

This new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. **VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.**

Concomitant with the research investigations of CCP and Remdesivir, the monoclonal antibodies of Ely Lilly and Regeneron were being researched this summer. Both companies in October 2020 requested that the FDA not include their research data from administrations in patients severely-affected by COVID-19 [Aside: The administrations of monoclonal antibodies to severely affected COVID-19 patients would generally have been out of the viremic phase and into the phase the NIH terms: an exaggerated immune/inflammatory response to the virus that leads to tissue damage.] I would speculate that the monoclonal antibodies showed the same mildly positive/poor results in the later stages of COVID-19 disease that the FDA reported in the CCP National Expanded Access Program of the Mayo Clinic. Thus, when Rear Admiral Hinton authorized the EUAs for the monoclonal antibodies, the authorizations read:

- 1. to Eli Lilly on November 10, 2020,
 - · The bamlanivimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
 - · Bamlanivimab is not authorized for use in the following patient populations 5:

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- · Adults or pediatric patients who are hospitalized due to COVID-19, or
- · Adults or pediatric patients who require oxygen therapy due to COVID-19, or
- · Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.

(https://www.fda.gov/media/143602/download)

2. to Regeneron on November 21, 2020,

- · The casirivimab and imdevimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
- · Casirivimab and imdevimab may only be administered together;
- · Casirivimab and imdevimab is not authorized for use in the following patient populations 5:
 - · Adults or pediatric patients who are hospitalized due to COVID-19, or
 - · Adults or pediatric patients who require oxygen therapy due to COVID19, or
 - · Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity

(https://www.fda.gov/media/143891/download)

Over the summer both convalescent plasma and remdesiver and monoclonal antibodies we're being given to individuals under the strict *Inclusion* Criteria. As such, the Mayo Clinic protocol in the distribution COVID-19 Convalescent Plasma could not be declared a "completed Phase I" study as it was *Expanded Access* even though 86,000 Americans received it safely. Without a "completed Phase I" trial confirmed by the FDA, the Right to Try law was not implemented.

Unfortunately, there has been too much politicking over the summer and fall of 2020 as to whether or not the agents are really effective. What is really relevant is that the research was performed late in the individual patient's course of the disease which is not the appropriate time to administer *Passive Immunization* and *Antiviral drugs*. The NIH's *Executive Summary* states that the appropriate time to administer Passive Immunization and Antiviral Drugs is as early as possible – not late in the patient's disease course. As stated in the FDA's executive summary, the antibodies and the antivirals therapies (e.g.: *Passive Immunization and Antiviral Drugs*) should be given early in the treatment of the disease of COVID-19--most appropriately within 72 hours of COVID-19 positivity. Dexamethasone, a steroid, should be administered when the patient demonstrates COVID-19 induced lung pathology.

The FDA recognized the underlying mistake/misassumption of the *inclusion severity criteria* and removed it officially on August 28, 2020 with regards to Remdesivir and on September 2, 2020 with regards to COVID-19 convalescent plasma. Both Eli Lilly and Regeneron recognized in the late summer or early fall that data from late administration of their monoclonal antibodies would cloud the issue. Thus, both companies petitioned the FDA to remove their data results regarding the administration of their respective monoclonal antibodies to patients that were severely affected by COVID-19. As was listed above, when the EUAs were authorized by the Chief Scientist of the FDA, the restrictions for administration of the monoclonal antibodies of Eli Lilly and Regeneron (*Passive Immunization*) were limited to outpatient therapy or hospitalized patients (admitted for other reasons than COVID-19) that were mild to moderately ill from COVID-19. With regards to Remdesivir, as you know from the October 22, 2020 NDA (NDA 214787), Remdesivir was authorized by the FDA as a new drug in the treatment of COVID-19 with the follow restrictions that are devoid of any pathophysiologic parameters:

VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care

My plea to you today is that you provide this message with the attachments to Secretary Wilke who can share this with the President's Coronovirus Taskforce. With the vaccines now available against COVID-19, prevention by *Active*

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Immunization will facilitate a more speedy and safer path to herd immunity rather than the present need for individual patient infections with COVID-19. Unfortunately, vaccination will not treat those unvaccinated that develop COVID-19 in the future. Without the antiviral treatments administered within ~72-120 hours of contraction of COVID-19 with Passive Immunization (COVID-19 Convalescent Plasma or monoclonal antibodies) and an antiviral agent like Remdesivir, those individuals that contract COVID-19 are relegated to a no-viral-treatment group of the COVID-19 virus which is de facto what has existed for the last 9 months!

As is stated in your VA profile, Dr. Stone, you are the Chief Medical Executive of the Veterans Health Aministration with the "...authority to perform the functions and duties of the Under Secretary for Health" of the VHA. The Under Secretary for Health (USH) has its foundations in the University-VA Affiliation of 1946 (PL 79-293) --then the *Director of Medicine, Surgery, and Psychiatry of the Veterans Administration*. The American veteran and the American people owe much to Dr. Hawley and Dr. Magnuson who with General Omar Bradley and President Truman advocated for the passage of what would become PL 79-293. Like the recent Under Secretaries of Health: Drs. Kizer, Garthwaite, Roswell, Perlin, Petzel, and Shulkin, you, first and foremost, are the Top Doctor for all individual Veteran patients. I, as a physician and surgeon of the VHA, have the privilege and honor to serve individual American veterans daily in the clinic, on the wards, and in the OR of the St. Louis (John Cochran) VAMC. You, as the USH of the VHA, have the privilege and honor to serve the individual American veteran in the aggregate. Let of us both strive to care for all the Veteran patients we are honored to serve by providing them with the appropriately timed (within 72-120 hours of COVID-19 positivity) administration of both *Passive Immunization* (e.g.: COVID-19 Convalescent Plasma or monoclonal antibodies) and an *Antiviral* (e.g.: Remdesivir) for that is our duty.

President Abraham Lincoln concluded his second inaugural address with that which established the concept of the VA and that which is most apropos in our nation's desperate fight against COVID-19:

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan – to do all which may achieve and cherish a just and lasting peace, among ourselves, and with all nations.

https://www.ourdocuments.gov/doc large image.php?flash=false&doc=38

Respectfully yours,

Charles H. Andrus, M.D., F.A.C.S.
Staff Surgeon, Surgical Service, St. Louis VAMC
Professor, Department of Surgery, Saint Louis University School of Medicine

Home phone: 314-455-9482 Beeper: 314-491-2417

Attachments:

- 1. Andrus CH: Time: The Crucial Independent Variable of the COVID-19 Pandemic. TXu002199029, June 8, 2020.
- 2. Andrus CH: Mayo Clinic "Safety Update" should be Classified as a Completed Phase I Trial of COVID-19 Convalescent Plasma. TXu002214049, July 22, 2020.
- 3. Andrus CH: A Plea for the Availability and Appropriate Administration of *Passive Immunization* against COVID-19 to All in the USA. Summitted to the U.S. Copyright Office, Library of Congress, November 17, 2020, copyright pending: case 1-9892777951.
- 4. Andrus CH: Letter to the Editor of NEJM. (Not yet sent as of 12-20-2020)

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From: Matthews, Kameron < Kameron. Matthews@va.gov>

Sent: Thursday, December 17, 2020 3:51 PM

To: Andrus, Charles H. (STL) < Charles.Andrus@va.gov>

Cc: Stone, Richard A., MD < <u>Richard.Stone2@va.gov</u>>; Echevarria, Kelly < <u>Kelly.Echevarria@va.gov</u>>

Subject: RE: Remdesivir

Dear Dr. Andrus,

Thank you for reaching out to leadership about VA's Remdesivir clinical guidance. We greatly appreciate your advocacy for your Veteran patients and your concern that VA's guidance may not be in alignment with other Remdesivir guidance. At Dr. Stone's request, I have reviewed the issues with our Pharmacy Benefits Management (PBM) colleagues.

As we have all seen, guidance for COVID-19 therapeutics can change rapidly as more experience with treatments is gained. We believe VA's November 20, 2020 guidance entitled "Remdesivir (VEKLURY): Criteria for Use" is based on the most recent evidence and is not inconsistent with guidance from other entities such as the National Institutes of Health.

VA's Criteria for Use (CFU) documents are not intended to merely reflect approval indication(s) by the Food and Drug Administration (FDA) but are intended to focus on optimal use—balancing data on efficacy and safety—of an agent for the *majority* of patients as based on available evidence. In this regard, it is not unusual for VA's guidance to differ from guidance from other organizations that was developed for purposes other than health care delivery. In that light, the current CFU coalesce and mirror the currently available evidence as elucidated by the National Institutes for Health's (NIH) "Therapeutic Management of Patients with COVID-19" and "Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19."

Specifically, VA's CFU directly address the group most likely to benefit from Remdesivir (i.e., hospitalized patients with COVID-19, requiring supplemental oxygen) which is consistent with the NIH guidance (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/):

"Remdesivir, an antiviral agent, is currently the only drug that is approved by the Food and Drug Administration for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.1-4" [italics added]"

And for hospitalized patients who do NOT require supplemental oxygen:

"There is insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate." [italics added]

Similarly, the Infectious Diseases Society of America (IDSA) does not recommend Remdesivir for hospitalized patients who do not need supplemental oxygen (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/):

"Recommendation 11: In patients with COVID-19 admitted to the hospital without the need for supplemental oxygen and oxygen saturation >94% on room air, the IDSA panel suggests against the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence)"

As such, regarding content, VA CFU recognize the careful balance that should be undertaken by clinicians in terms of using Remdesivir in patients who are NOT requiring supplemental oxygen as follows:

"*Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis".

This added statement thus mirrors the NIH guidance AND reflects the caution urged by IDSA. That is, it allows for use in patients with mild to moderate disease (i.e., not needing supplemental oxygen) BUT makes explicit that there should be careful consideration (and in practice most likely expert consultation) as to whether Remdesivir should be used for a specific individual patient with mild to moderate disease.

VA's CFU are meant to be guidance tailored and understood in a wholistic manner for a given patient and recognize that not all patients will fit into a given guideline. To that end, all CFU documents include the following statement:

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"The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES."

In practice this means that local clinicians should work with local Pharmacy & Therapeutics Committee (and/or delegates) to determine if a CFU document might not fit a specific patient. I understand that this process was followed and that Infectious Disease staff at your facility reviewed your specific request for Remdesivir and determined that it was not indicated.

The current VA CFU reflect evidence and are similar to guidance provided by the NIH and the IDSA and, as such, principally focus on optimal use (i.e., those most likely to benefit, meaning hospitalized patients requiring supplemental oxygen) yet still ALLOW for considered use in other patients—often in consultation with other experts (as necessary) and/or working with local P&T Committee (or delegates) to tailor use for an individual patient(s) with COVID-19. This balance should enable clinicians and VA's to provide the highest quality of care available for our hospitalized patients with COVID-19.

I hope this response addresses your concerns and I again thank you for taking the time to write.

Sincerely, Kameron

Kameron Leigh Matthews, MD, JD, FAAFP
Chief Medical Officer and Assistant Under Secretary for Health for Clinical Services
Veterans Health Administration | U.S. Department of Veterans Affairs
kameron.matthews@va.gov | (202) 461-4240 | Scheduling and Information: Christine Going and Tasha Martin

From: Andrus, Charles H. (STL) < Charles.Andrus@va.gov>

Sent: Tuesday, December 15, 2020 4:43 PM **To:** Echevarria, Kelly; Compton, Leslie R. (STL)

Cc: McDonald, Jay R. (STL); George, Sarah L. (STL); candrus600@aol.com; charles.andrus@health.slu.edu; Zacher,

Jennifer L. (PBM); Stone, Richard A., MD

Subject: RE: Remdesivir

12/15/2020

Kelly Echevarria, PharmD, BCPS, AQ-ID Manager, National Clinical Pharmacy Program Manager VA Pharmacy Benefits Management Services 10PAP

Dear Dr. Echevarria:

Thank you very much for your extensive response. Unfortunately, your reply e-mail has confirmed a significant contradiction between the VA Medical Advisory Panel and the Executive Summary of the NIH Therapeutic Management of Patients with COVID-19 (last updated, December 3, 2020) which you sent to me in your e-mail hyperlink: "here" (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/) in which in the executive summary it is stated:

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Search

Therapeutic Management of Patients with CO\

Last Updated: December 3, 2020

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the disease is primarily driven by replication of severe acute respiratory syndrome coronavirus CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflar response to the virus that leads to tissue damage. Based on this understanding, it is anticipate therapies would have the greatest effect early in the course of disease, while immunosuppress inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

You also included as an attachment another hyperlink: <u>Remdesivir Criteria for Use</u> in which the following is stated as the only Inclusion Criteria for Remdesivir authorized by VACO:

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Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dy and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-m to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THE GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURE ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://voww.pbm.va.gov for further information.

Ex	clusion Criteria
If th	e answer to ANY item below is met, then the patient should NOT receive remdesivir
	Treated for COVID-19 as an outpatient
	AST or ALT > 5 times the upper limit of normal
	Hospitalized patients but NOT requiring supplemental oxygen*
	Concomitant use of hydroxychloroquine or chloroquine
	Current eGFR < 30 mL/min**
Ine	clusion Criteria
The	following must be fulfilled in order to meet criteria for remdesivir
	Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***

This is **absolutely contradictory to the NIH Executive Summary Above** regarding the pathophysiology of COVID-19 and the therapeutic recommendations: "...it is anticipated that antiviral therapies would have greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19." Internally, though, what follows in the NIH Executive Summary is completely contradictory to the NIH's first paragraph. (Obviously, the NIH needs to deal with this.)

The VA Remdesivir Criteria for Use has now brought this to light. By this misinterpretation of the timing of administration of Remdesivir by the VA Pharmacy Panel (the FDA removed the severity criteria on August 28, 2020—the chronological history of the removal of the severity criteria is outlined in Rear Admiral Hinton's EUA on Remdesivir of October 22, 2020.), has condoned *de facto* discrimination against any Veteran patient who presents COVID-19 positive BUT without severe symptoms early in the course of his/her disease. Please provide this entire correspondence to the VA National Clinical Pharmacy Panel. The panel should probably decide whether this should also be provided to the Office of VA General Counsel and the VA Office of the Inspector General. Due to the seriousness of these contradictions and probably a condoned discrimatory practice by the VHA toward individual Veterans early-in-the-course of their COVID-19 disease, I will include Dr. Stone as he is the Executive in Charge, VHA, in this correspondence.

Sincerely,

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Charles H. Andrus, M.D., F.A.C.S.
Professor, Department of Surgery, Saint Louis University School of Medicine
Attending General Surgeon, Unit II (SLU) General Surgery, Surgical Service (112-JC), St. Louis (John Cochran) VAMC
314-652-4100 ext 54463
Beeper 314-491-2417

From: Echevarria, Kelly < Kelly. Echevarria@va.gov>

Sent: Tuesday, December 15, 2020 9:43 AM

To: Andrus, Charles H. (STL) < <u>Charles.Andrus@va.gov</u>>; Compton, Leslie R. (STL) < <u>Leslie.Compton@va.gov</u>> **Cc:** McDonald, Jay R. (STL) < <u>Jay.McDonald1@va.gov</u>>; George, Sarah L. (STL) < <u>Sarah.George@va.gov</u>>; candrus600@aol.com; charles.andrus@health.slu.edu; Zacher, Jennifer L. (PBM) < <u>Jennifer.Zacher@va.gov</u>>

Subject: RE: Remdesivir

Home phone: 314-455-9482

Good morning sir,

As you stated remdesivir was formally approved by the FDA as follows: indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

That being said, the VA National Formulary Committee reviews every new drug, including all data to determine the safest, most effective and most cost-effective way to use that product within the VA. Materials such as the drug monograph are developed for discussion and if deemed necessary to ensure safe and appropriate use, Criteria For Use are sometimes also developed that are evidence based but may not match the FDA indication exactly. This multi-disciplinary committee votes on formulary status and criteria after circulating draft documents to clinicians in the field for comments and suggestions.

In the case of remdesivir, the data is inconsistent, with ACTT-1 showing benefit primarily in the subpopulation of patients requiring supplemental oxygen at baseline. Patients hospitalized but not requiring oxygen, and those on mechanical ventilation or ECMO did not derive a significant benefit from remdesivir in this setting. In addition, when the data was looked at by separating mild-moderate disease from severe, only the severe group had a significant benefit in terms of outcome.

The moderate SIMPLE trials from Gilead was open label and compared 5 vs. 10 days of remdesivir vs. no therapy and although 5 days was associated with clinical benefit (more likely to have improved clinical status at day 11) but the 10 day group did not, and confidence intervals were wide. The severe SIMPLE trial is largely uninterpretable for safety or efficacy as there was no standard of care arm.

The NIH COVID-19 guidelines generally do not recommend remdesivir for patients not requiring oxygen or for those ill enough to require invasive mechanical ventilation or ECMO, although there may be cases where it is appropriate, such as very high risk patients or those rapidly progressing. Their treatment algorithm can be found here. The WHO doesn't recommend remdesivir at all given the somewhat conflicting data and the SOLIDARITY trial not showing evidence of benefit.

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The VA Criteria for use and drug monograph are below and were approved after field comments, and approval by the VPE/MAP national formulary committee. Essentially anyone requiring oxygen, with a room air saturation < 94% or other indicators of severe disease is eligible provided they do not have exclusions. There may be situations, which can be adjudicated on a case by case basis where the benefit may be felt to outweigh the risks by the ordering provider, but as a general rule, given the lack of benefit in the subpopulation not requiring supplemental oxygen, it isn't routinely recommended. The Committee voted to add remdesivir to formulary as a Prior Authorization product at the facility level with the criteria for use below.

Please let me know if you have any additional questions or comments that I can address. A request for a change of CFU or formulary status can be taken through the local facility P&T to the VISN P&T and then to the National Formulary Committee if desired.

Remdesivir drug monograph

Remdesivir Criteria for Use

From: Andrus, Charles H. (STL) < Charles.Andrus@va.gov>

Sent: Monday, December 14, 2020 2:28 PM

To: Compton, Leslie R. (STL) < Leslie.Compton@va.gov >

Cc: McDonald, Jay R. (STL) < <u>Jay.McDonald1@va.gov</u>>; George, Sarah L. (STL) < <u>Sarah.George@va.gov</u>>; Echevarria, Kelly

< <a href="mai

charles.andrus@health.slu.edu

Subject: RE: Remdesivir

12/14/2020

Dear Drs. Compton, McDonald, George, and Echevarria:

Attached are excerpts from the FDA EUAs regarding Remdesivir to the present by Rear Admiral Hinton, R.N., M.S., Chief Scientist, U.S. Food & Drug Administration. I am forwarding the attachment to all of you to document what is in the August 28, 2020- EUA for Remdesivir by the FDA: "...FDA is reissuing the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease." With the issuing of approval on October 22, 2020 of the NDA 214787 for remdesivir, John Farley, MD, MPH, Director, Office of Infectious Diseases, Center for Drug Evaluation and Research, U.S. FDA stated: "This new drug application provides for the use of VEKLURY (remdesivir) injection and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighting at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care." Dr. Farley did not reinstate nor insert any of the previous "severity criteria" that had been removed by Rear Admiral Hinton on August 28, 2020.

Sincerely,

Charles H. Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine

Staff Surgeon, Chief, Unit II General Surgery, Surgical Service, St. Louis (John Cochran) VAMC (112jc), 915 N Grand Blvd,

St. Louis, MO

Office: 314-652-4100 ext: 54463

Beeper: 314-491-2417

From: Compton, Leslie R. (STL) < Leslie.Compton@va.gov>

Sent: Thursday, December 10, 2020 2:34 PM

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To: Andrus, Charles H. (STL) < Charles.Andrus@va.gov>

Subject: Remdesivir

Good afternoon, Dr. Andrus. I got your voicemail and wanted to follow up. While Veklury (remdesivir) was approved by the FDA, we still have to comply with the VA National Formulary, which indicates criteria for use must be met for remdesivir use. I have attached the criteria for use if you are interested.

Thank you Leslie Compton, PharmD Pharmacy Operations Manager VA St. Louis Health Care System John Cochran Division

Phone: 314-652-4100 ext 56338

December 20, 2020

Richard A. Stone, M.D.

Executive in Charge, Veterans Health Administration (VHA)

("Authority to Perform the functions and duties of the Under Secretary for Health"

https://www.va.gov/opa/bios/bio_stone.asp)

Dear Dr. Stone:

I thank you so much for participating and taking interest in my submissions to you last week regarding Remdesivir. I also appreciate the response that has been provided to me and you by Dr. Matthews at your request. Unfortunately, what has occurred has been based on a series of misadventures that were initiated in March 2020 by the U.S. Food and Drug Administration (FDA), the National Institutes for Health (NIH), the President's Coronavirus Taskforce, etc. that have led to confusion in treating COVID-19.

Included in Dr. Echevarria's initial response e-mail to me was a hyperlink to the National Institutes of Health COVID-19 Guidelines Panel's Treatment Guidelines. The first paragraph of the *Executive Summary* nicely outlines the pathophysiology of COVID-19 with an initial viremia and the subsequent COVID-19 positive patient's development of an out-of-control immunologic response resulting in pneumonia, SARS, and possibly multisystem organ failure:

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome cononavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

In March 2020, the FDA and in the Presidential Coronavirus Taskforce was presented with a dilemma: they knew that for 120 years one of the methodologies utilized in the treatment of any new (novel) virus was the noble-prize winning concept of **Passive Immunization** but the USA had few COVID-19-recovered convalescent patients to provide plasma which is the frontline agent in the administration of **Passive Immunization**. **Passive Immunization** is the use of immunoglobulins (that is neutralizing antibodies) as a temporizing immunologic treatment as antibodies attach to the antigens of the virus particle thus inhibiting some of the effects of the virus on the infected patient. **Passive Immunization** has been used successfully over the years with regards to Rabies and other infectious diseases and as antivenoms against snakebites, etc. The most successful example of **Passive Immunization** is RhoGAM: Providing postpartum mothers who are Rh negative within 72 hours of delivery of a Rh-positive baby with antibodies to neutralize and lyse fetal RBCs acquired by the mother during delivery. Approved by the FDA in 1968, RhoGAM has essentially made *hydrops fetalis* a disease of history in the USA. The other therapeutic agent mentioned in the NIH *Executive Summary* was the development of an antiviral agent effective against the coronavirus (e.g.: Remdesivir).

In March 2020, the first misadventure that occurred was the FDA's failure to declare COVID-19 convalescent plasma a *biosimilar* biologic. COVID-19 Convalescent Plasma (CCP) is nothing more than fresh frozen plasma (FFP), which is available from every Blood Bank, that specifically has been obtained from a patient that has recovered from the disease. As a general surgeon over the years, I have used countless FFP units in the resuscitation of patients with bleeding diatheses or exsanguinating from penetrating trauma, motor vehicle accidents, etc. FFP is fresh frozen (< -30° C) plasma--the serum component of every unit of blood. As such, the FDA, not the NIH or any other branch of the Federal Government has the sole statutory authority and responsibility for every blood component and every aspect of every Blood Bank in the USA, blood collection techniques, blood processing and assaying techniques, and blood administration in the United States. As such, the mechanism for collection, processing and distribution of COVID-19 Convalescent Plasma has been and is already in place under the statory auspices of the U.S. Food and Drug Administration (FDA).

Unfortunately, COVID-19 Convalescent Plasma (CCP) was deemed by the FDA *Investigational*. Anytime a drug or biologic is deemed *Investigational* by the FDA, a formal Clinical Trials process is initiated (see NIH https://www.clinicaltrials.gov/) mandating Phase 1 (a safety trial) and subsequently Phase 2 and 3 (efficacy trials) in the evaluation of a new drug or biologic. Therefore, the FDA established its *inclusion criteria* for Phase 1 clinical trials [safety only] and publicly announced the criteria in all its documentation on April 8, 2020, as in: Recommendations for Investigational COVID-19 Convalescent Plasma (<a href="https://web.archive.org/web/20200408215026/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma):

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol . These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - o Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio <
 300,
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

Normally, Phase 1 Clinical Trials according to the FDA should include 12 to 20 individuals. In a rush to provide easy access to CCP, the FDA announced in early April 2020 a collaboration with

the Mayo Clinic in the National Expanded Access Treatment Protocol without the FDA assuming any responsibility as the little box with the arrow is the FDAs hyperlink to the FDA external disclaimer website. Unfortunately, under the Mayo Clinic COVID-19 Convalescent Plasma protocol website almost 95,000 units of CCP have been safely administered which could not be used as data for declaring a "Completed Phase 1 trial" due to its designation as under Expanded Access. Expanded Access = Compassionate Use precludes any research entity to use data from any compassionate use protocol. All clinical research in the USA is scrutinized by Investigational Research Boards (IRBs), and all IRBs are exclusively overseen and regulated by the FDA. Thus, the FDA could not declare CCP safe by a "Completed Phase 1 trial." Why is this so important? – because the only stipulation for the implementation of the Federal Law enacted by Congress and signed into law by the President of the United States in 2018, The Right to Try Act of (PL-115-176) is that a "Completed Phase 1 trial" be acknowledged. In essence, agencies of the U.S. Department of Health and Human Services have violated the intent of Federal Law by circumventing a "Completed Phase 1 Trial" with the present disastrous results.

The EUA for Remdesivir was first authorized by Rear Admiral Hinton, FDA Chief Scientist, on May 1, 2020 with similar strict *Inclusion* eligibility criteria as was applied to CCP. https://web.archive.org/web/20200501204823/https://www.fda.gov/media/137564/download. The history of this rescinding of the severity criteria regarding Remdesivir on August 28, 2020 was reported in Rear Admiral Hinton's EUA update of October 22, 2020 https://www.fda.gov/media/137564/download which coincided on the same day of the FDA issuing a New Drug Authorization (NDA 214787) for Remdesivir by John J. Farley, MD, MPH, Director, Office of Infectious Diseases, Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/2147870rig1s000ltr.pdf
Without any physiology restrictions except for hospitalization, the FDA stated:

NDA 214787

NDA APPROVAL

Gilead Sciences, Inc. Attention: Ashley Rhoades, MBS, RAC Manager, Regulatory Affairs 333 Lakeside Drive Foster City, CA 94404

Dear Ms. Rhoades:

Please refer to your new drug application (NDA) dated and received August 7, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VEKLURY (remdesivir) injection, 5 mg/mL; VEKLURY (remdesivir) for injection, 100 mg/vial.

This new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

Concomitant with the research investigations of CCP and Remdesivir, the monoclonal antibodies of Ely Lilly and Regeneron were being researched this summer. Both companies in October

2020 requested that the FDA not include their research data from administrations in patients severely-affected by COVID-19 [Aside: The administrations of monoclonal antibodies to severely affected COVID-19 patients would generally have been out of the viremic phase and into the phase the NIH terms: an exaggerated immune/inflammatory response to the virus that leads to tissue damage.] I would speculate that the monoclonal antibodies showed the same mildly positive/poor results in the later stages of COVID-19 disease that the FDA reported in the CCP National Expanded Access Program of the Mayo Clinic. Thus, when Rear Admiral Hinton authorized the EUAs for the monoclonal antibodies, the authorizations read:

1. to Eli Lilly on November 10, 2020,

- The bamlanivimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
- Bamlanivimab is not authorized for use in the following patient populations ⁵:
 - Adults or pediatric patients who are hospitalized due to COVID-19, or
 - Adults or pediatric patients who require oxygen therapy due to COVID-19, or
 - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.

(https://www.fda.gov/media/143602/download)

2. to Regeneron on November 21, 2020,

- The casirivimab and imdevimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
- Casirivimab and imdevimab may only be administered together;
- Casirivimab and imdevimab is not authorized for use in the following patient populations ⁵:
 - Adults or pediatric patients who are hospitalized due to COVID-19, or
 - Adults or pediatric patients who require oxygen therapy due to COVID19, or
 - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity

(https://www.fda.gov/media/143891/download)

Over the summer both convalescent plasma and remdesiver and monoclonal antibodies we're being given to individuals under the strict *Inclusion* Criteria. As such, the Mayo Clinic protocol in the distribution COVID-19 Convalescent Plasma could not be declared a "completed Phase I" study as it was *Expanded Access* even though 86,000 Americans received it safely. Without a "completed Phase I" trial confirmed by the FDA, the Right to Try law was not implemented.

Unfortunately, there has been too much politicking over the summer and fall of 2020 as to whether or not the agents are really effective. What is really relevant is that the research was performed late in the individual patient's course of the disease which is not the appropriate time to administer *Passive Immunization* and *Antiviral drugs*. The NIH's *Executive Summary* states that the appropriate time to administer Passive Immunization and Antiviral Drugs is as early as possible – not late in the patient's disease course. As stated in the FDA's executive summary, the antibodies and the antivirals therapies (e.g.: *Passive Immunization and Antiviral Drugs*) should be given early in the treatment of the disease of COVID-19--most appropriately within 72 hours of COVID-19 positivity. Dexamethasone, a steroid, should be administered when the patient demonstrates COVID-19 induced lung pathology.

The FDA recognized the underlying mistake/misassumption of the *inclusion severity criteria* and removed it officially on August 28, 2020 with regards to Remdesivir and on September 2, 2020 with regards to COVID-19 convalescent plasma. Both Eli Lilly and Regeneron recognized in the late summer or early fall that data from late administration of their monoclonal antibodies would cloud the issue. Thus, both companies petitioned the FDA to remove their data results regarding the administration of their respective monoclonal antibodies to patients that were severely affected by COVID-19. As was listed above, when the EUAs were authorized by the Chief Scientist of the FDA, the restrictions for administration of the monoclonal antibodies of Eli Lilly and Regeneron (*Passive Immunization*) were limited to outpatient therapy or hospitalized patients (admitted for other reasons than COVID-19) that were mild to moderately ill from COVID-19. With regards to Remdesivir, as you know from the October 22, 2020 NDA (NDA 214787), Remdesivir was authorized by the FDA as a new drug in the treatment of COVID-19 with the follow restrictions that are devoid of any pathophysiologic parameters:

VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care

My plea to you today is that you provide this message with the attachments to Secretary Wilke who can share this with the President's Coronovirus Taskforce. With the vaccines now available against COVID-19, prevention by *Active Immunization* will facilitate a more speedy and safer path to herd immunity rather than the present need for individual patient infections with COVID-19. Unfortunately, vaccination will not treat those unvaccinated that develop COVID-19 in the future. Without the antiviral treatments administered within ~72-120 hours of contraction of COVID-19 with *Passive Immunization* (COVID-19 Convalescent Plasma or monoclonal antibodies) and an antiviral agent like Remdesivir, those individuals that contract COVID-19 are relegated to a no-viral-treatment group of the COVID-19 virus which is *de facto* what has existed for the last 9 months!

As is stated in your VA profile, Dr. Stone, you are the Chief Medical Executive of the Veterans Health Aministration with the "...authority to perform the functions and duties of the Under Secretary for Health" of the VHA. The Under Secretary for Health (USH) has its foundations in the University-VA Affiliation of 1946 (PL 79-293) --then the *Director of Medicine, Surgery, and Psychiatry of the Veterans Administration*. The American veteran and the American people owe much to Dr. Hawley and Dr. Magnuson who with General Omar Bradley and President Truman advocated for the passage of what would become PL 79-293. Like the recent Under Secretaries of Health: Drs. Kizer, Garthwaite, Roswell, Perlin, Petzel, and Shulkin, you, first and foremost,

are the Top Doctor for all individual Veteran patients. I, as a physician and surgeon of the VHA, have the privilege and honor to serve individual American veterans daily in the clinic, on the wards, and in the OR of the St. Louis (John Cochran) VAMC. You, as the USH of the VHA, have the privilege and honor to serve the individual American veteran in the aggregate. Let of us both strive to care for all the Veteran patients we are honored to serve by providing them with the appropriately timed (within 72-120 hours of COVID-19 positivity) administration of both *Passive Immunization* (e.g.: COVID-19 Convalescent Plasma or monoclonal antibodies) and an *Antiviral* (e.g.: Remdesivir) for that is our duty.

President Abraham Lincoln concluded his second inaugural address with that which established the concept of the VA and that which is most apropos in our nation's desperate fight against COVID-19:

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan – to do all which may achieve and cherish a just and lasting peace, among ourselves, and with all nations.

 $\underline{https://www.ourdocuments.gov/doc_large_image.php?flash=false\&doc=38}$

Respectfully yours,

Charles H. Andrus, M.D., F.A.C.S. Staff Surgeon, Surgical Service, St. Louis VAMC Professor, Department of Surgery, Saint Louis University School of Medicine Home phone: 314-455-9482

Beeper: 314-491-2417

Attachments:

- 1. Andrus CH: Time: The Crucial Independent Variable of the COVID-19 Pandemic. TXu002199029, June 8, 2020.
- 2. Andrus CH: Mayo Clinic "Safety Update" should be Classified as a Completed Phase I Trial of COVID-19 Convalescent Plasma. TXu002214049, July 22, 2020.
- 3. Andrus CH: A Plea for the Availability and Appropriate Administration of *Passive Immunization* against COVID-19 to All in the USA. Summitted to the U.S. Copyright Office, Library of Congress, November 17, 2020, copyright pending: case 1-9892777951.
- 4. Andrus CH: Letter to the Editor of NEJM. (Not yet sent as of 12-20-2020)

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55.0 541 Letter to NEJM editor 12 13-2020 (1) copy.pdf

December 13, 2020

Dear NEJM editor:

The USA SARS-CoV-2 virus (COVID-19) epidemic continues to progress towards herd immunity¹ necessitating individually $\sim 70\%$ of USA population (~ 332 million x 0.7) to either contract and hopefully survive COVID-19 infection or be administered preemptive *Active Immunization* through two vaccine doses a month apart--soon to be available.²⁻⁴ Unfortunately, once an unvaccinated individual contracts COVID-19 though, immediate vaccination will not be beneficial due to the physiologic time delay in the development of neutralizing antibodies. ^{5,6} Unlike China's utilization of *Passive Immunization* in the form of early COVID-19 Convalescent Plasma (CCP) administration to diminish their epidemic (China offered 90 tons of CCP to Italy in March 2020)⁷, the USA has publicly downplayed the potential of *Passive* **Immunization** in the early treatment of COVID-19 positivity. The New England Journal of Medicine (NEJM) article of 11/24/2020 by Simonovich et al entitled: A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia⁸ correctly and outstandingly has confirmed and concluded the medically-obvious ineffectiveness of COVID-19 Convalescent Plasma (or any passive immunity agent) administered at the wrong time (not until SARS severe pneumonia symptomatology was expressed) due to failure of early-in-the-course-of-the-disease empiric therapy consistent with the pathophysiology. ^{9,10} Unfortunately, in the abstract's conclusion statement, the authors of the present NEJM article failed to include "in Covid-19" severe pneumonia" which has led to erroneous generalizations and comments 11 about the efficacy of CCP⁸ in all COVID-19 positive patients:

No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. (PlasmAr ClinicalTrials.gov number, NCT043833535.).

As with all convalescent plasmas and sera, to be maximally effective, CCP should be administered as early as possible as an immune therapy agent to diminish the length and intensity of the viremia-- within 72 hours of COVID-19 confirmed positivity before SARS symptomatology becomes pronounced. Early administration for viremia modulation of both *Passive Immunization* (e.g.: CCP) and Remdesivir have been consistently confused this summer with steroid therapy (dexamethasone). Dexamethasone administration is postulated to modulate the inflammatory-mediated lung injury / cytokine storm (SARS pneumonia) and does not affect the initial SARS-CoV-2 viremia. In issuing on August 23, 2020 and reissuing on November 30, 2020 the Emergency Use Authorization (EUA) for CCP, FDA Chief Scientist, RADM Dennis Hinton, R.N., M.S., emphasized the correct importance of CCP administration "early in the course of disease" but **incorrectly** advised continuing the late-CCP-administration practice in the ongoing clinical reseach trials.

Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of disease. COVID-19 convalescent plasma units containing antibodies to SARS-CoV-2 but not qualified as high-titer by a test found acceptable for this purpose by FDA (see Section II) are considered Low Titer units and are acceptable for use based on an individualized assessment of patient benefit-risk. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of COVID-19 convalescent plasma efficacy and to determine the optimal product attributes and appropriate patient populations for its use. Given that the clinical evidence supporting this EUA was

not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs are needed. COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Additional data will be forthcoming from other analyses and ongoing, well-controlled clinical trials in the coming months. These ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on the issuance of this EUA; providers are encouraged to enroll patients in those trials.

The patient *Eligibility Criteria* applied in the presently-reported clinical study in NEJM⁸ and the majority of clinical trials registered in NIH ClinicalTrials.gov¹⁸ prior to September 2, 2020, was a restrictive, end-of-life criteria published by the U.S. Food and Drug Administration (FDA) for the anticipated Phase I safety clinical trials of COVID-19 convalescent plasma initiated in March 2020. This FDA proclaimed patient *Eligibility Criteria* was the underlying guiding *de facto* policy officially from April 8, 2020¹⁹ to September 1, 2020²⁰ [146 days] in which its UNIVERSIAL LATE-ADMINISTRATION-OF-CCP WAS A MISTAKE. Without any elaboration, the FDA <u>rescinded the patient *Eligibility Criteria* by removing it from all future FDA documentation quietly on September 2, 2020.

The elimination of the following restrictive, late-in-the-clinical-disease administration of CCP was NOT widely proclaimed by the FDA to the medical community, medical-research establishment, and the American public at large when it was implemented by unannounced omission on September 2, 2020²¹:</u>

Patient Eligibility^{19,20}

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the **National Expanded Access**Treatment Protocol²³ ** (https://www.uscovidplasma.org/)²³, discussed in section III.A. of this guidance. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example, o Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency $\geq 30/\min$,
 - blood oxygen saturation $\leq 93\%$,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
 - lung infiltrates > 50% within 24 to 48 hours o Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

With the issuing of the Emergency Use Authorization (EUA) for COVID-19 Convalescent Plasma by Rear Admiral Hinton, RN, MS, Chief Scientist of the FDA, on

August 23, 2020¹⁶, the limitation to <u>only hospitalized</u> patients at potentially death's door <u>was continued and sustained</u>. The FDA's surreptitious-rescinding electronic Internet overwrite²¹ of the inappropriate CCP-late-administration-timed *Eligibility Criteria*^{19,20} on September 2, 2020²¹ without a substantive public media notification was 1) a dereliction-to-duty by the FDA and 2) a discriminatory denial of early administration of COVID-19 Convalescent Plasma to patients in the outpatient, nursing home, or assistant (*sic* assisted) living venues by the U.S. Federal Government.²⁵

This restrictive patient *Eligibility Criteria* was perpetuated over the spring and summer of 2020 by the FDA failing to declare the >86,000 CCP infusion in the Mayo Clinic's Expanded Access Program (EAP)²⁶ a "*completed*" Phase I safety trial.²⁷ The reasoning was outlined by the NIH COVID-19 Treatment Guidelines Panel²⁸:

The Mayo Clinic's Expanded Access Program (EAP) was developed in parallel to provide broader access to convalescent plasma; however, it was not designed to generate definitive data on safety or to evaluate efficacy (13). One of the requirements for an EAP is that it not interfere with pivotal trials (14). Adequately powered RCTs of convalescent plasma in the United States have been slow to enroll patients.

By not *de facto* declaring the Mayo Clinic's Expanded Access Program (EAP)²⁶ (technically not a Phase I Clinical Trial by NIH ClinicalTrials.gov definition¹⁸) a "completed" Phase I safety trial, the FDA circumvented statutory intent of Public Law 115-176, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act.²⁹ The erroneously-timed-FDA-directed *Eligibility Criteria* that was quietly omitted by the FDA on September 2, 2020²¹ has been perpetuated as a *de facto* prohibition of the <u>early</u> application of *Passive Immunization* (CCP) in the treatment <u>all</u> individuals developing COVID-19 positivity. This misdirection of the <u>early</u> application of *Passive Immunization* (CCP) in the treatment of <u>all</u> individuals developing COVID-19 positivity by the FDA omission has been legitimated continued research at the wrong time by 1.) RADM Hinton's reauthorization of the CCP EUA on November 30, 2020¹⁷ and 2.) the misinterpretation of COVID-19-late-administration-timing by the U.S. National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel.^{28,30-32}

1.) Pertinent excerpts from RADM Hinton's reauthorization of the CCP EUA¹⁷ on November 30, 2020:

Having concluded that the criteria for issuance of this authorization under 564(c) of the Act are met, I am authorizing the emergency use of COVID-19 convalescent plasma for treatment of hospitalized patients with COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19 when administered as described in the Scope of Authorization (Section II) meet the criteria for issuance of an authorization under Section 564(c) of the Act, because:

⁴ A national expanded access protocol (EAP) sponsored by the Mayo Clinic was established in April 2020 and enrolled >100,000 subjects. The EAP discontinued enrollment in August 2020, following the issuance of the EUA for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The goal of this uncontrolled, single-arm study was to provide access to COVID-19 convalescent plasma in hospitalized subjects with severe or life-

threatening COVID-19 or judged by the treating provider to be at high risk of progression to severe or life-threatening disease.

⁵ Information derived from ongoing clinical trials of COVID-19 convalescent plasma (particularly randomized controlled trials), as well as clinical trial results from studies of other investigational medical products to treat COVID-19, will continue to inform the risk-benefit assessment for this EUA.

Page 3—Dr. Kadlec, ASPR

- 1. SARS-CoV-2 can cause COVID-19, a serious or life-threatening disease or condition, including severe respiratory illness, in humans infected by this virus;
- 2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that COVID-19 convalescent plasma may be effective in treating COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of COVID-19 convalescent plasma when used to treat COVID19 outweigh the known and potential risks of such products; and
- 3. There is no adequate, approved, and available alternative to the emergency use of COVID-19 convalescent plasma for the treatment of COVID-19.6,7

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The emergency use of the authorized COVID-19 convalescent plasma under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below

2.) Pertinent excerpts from the NIH COVID-19 Treatment Guidelines Panel of October 9, 2020³¹:

Convalescent Plasma.

Last Updated: October 9, 2020

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.

Recommendation

 There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was **designed primarily to provide broad access to investigational convalescent plasma and thus** *did not include an untreated control arm*. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes

than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance. ^{2,3} Despite meeting the "may be effective" criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population. ^{4,5} Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing. The Panel's assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents.

Excerpts from EUAs for the **Passive Immunization agents:** i.e., COVID-19 Convalescent Plasma and the Monoclonal Antibodies (Appendix 1: Excerpts regarding Patient Eligibility for Agents of Passive Immunization); and excerpts from the EUAs and NDA #214787 for the antiviral agent Remdesivir (Appendix 2: Remdesivir EUAs and NDA #214787) are attached to this Letter to the Editor.

In a rush to develop a vaccine (which is <u>not a treatment nor cure</u> but preventive *Active Immunization* against a virus like COVID-19)²⁻⁴, the most important multifactorial independent elements that collectively result in the severe morbidity and mortality in *COVID-19 infected individuals* have been misaddressed and publicly ignored in a less-than-coordinated, leaderless treatment methodology for nine months regarding: age-related mortality^{33,34} *versus TIME* to intrinsic neutralizing antibody development after infection or vaccination (*Active Immunization*)³⁵⁻³⁷, time-length of the viremia and possible modification/modulation with <u>early administration</u> with *Passive Immunization*¹²⁻¹³, and the subsequent time to SARS sequelae and fatality. When both President Trump and former Governor Christy were given *Passive Immunization* early-in-the-course-of-the-disease treatment, both experienced very successful, outstanding outcomes from the COVID-19 treatment³⁸ which <u>should be available to the general public</u> and **NOT** just to <u>those of privilege.</u>³⁹ The logic of early treatment of COVID-19 was summarized as in *The New York Times*, October 3, 2020³⁸:

COVID-19 has two phases in those who become severely ill, said Dr. Robert Finberg, professor and chair of the department of medicine at the University of Massachusetts Medical School.

First, the virus replicates, and then the immune system overreacts to the virus, creating a different sort of illness that can be hard to control. Chemicals released by white blood cells can result in severe inflammation of organs, especially the lungs and heart, a reaction that can be fatal.

Both monoclonal antibodies and remdesivir attack the virus, Finberg added, so it should be best to use them early on while the disease is still caused by the virus itself.

Non-implementation and timely-inappropriate-late-administration of the empiric, biosimilar immunotherapy of COVID-19 Convalescent Plasma (Passive Immunization) before the severe symptoms of SARS become irreparable is the embodiment of much of that which is wrong. The inappropriate administration of too-late-in-the-disease combined with the misinterpretation of "Expanded Access" (really "compassionate use" only) became a research stumbling block of semantics for the FDA and the NIH in the clinical research analyses of COVID-19 Convalescent Plasma! "Expanded Access" does not mean easy access but rather defines a methodology of circumventing the standard research outcomes evaluation (NIH ClinicalTrials.gov of an investigational drug or biologic making the outcomes unsuitable for appropriate research analyses and conclusions. That is why, in a segment of the quote from the NIH COVID-19 Guidelines panel above, the NIH COVID-19 Treatment Guidelines panel, publishing Medical Researchers, and many of the agencies of the U.S. Department of Health and Human Services have confused definitions and terminology (e.g. efficacy versus safety, expanded access/compassionate use versus clinical trials, the Expanded Access Program (EAP) versus Phase I [safety]/Phase II or III [efficacy] clinical trials) creating a word-salad of obfuscation:

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to **evaluate** the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's **Expanded Access** Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data [FDA used this to justify the EUA regarding COVID-19 Convalescent Plasma again on 9/23/2020]⁴², hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers.

Medical researchers and Governmental insistence on confusing **safety versus efficacy** and the absolutism of rigorous **Phase II/III efficacy studies without a "completed official Phase I safety study"** after greater than >70,000 CCP units have been safely administered under Expanded Access⁴¹ *at-the-wrong-time* has impeded the appropriate empiric implementation of CCP and has evaded the intent of *The Right to Try Act.*²⁹ Strict adherence demanding *efficacy studies* when Placebo Controls in Randomized Prospective Studies are employed when there are **NO** alternate treatments available and severe morbidity and mortality are predictable is *UNETHICAL* ^{43,44} Withholding of a safe, empiric therapy from the individual in the presence of a potentially fatal disease outcome is synonymous to violations of the intent of *The Nuremberg Code, Declaration of Helsinki*, and *The Belmont Report.*⁴⁵ The Federal Government condoning the *de facto* withholding of COVID-19 Convalescent Plasma is tantamount to the *Tuskegee Syphillis Study* applied at a *de facto* national level.^{37,46} In essence, our society on the World's stage has demonstrated all-too-often in the last nine months the first four stages of Elisabeth Kübler-Ross's *On Death and Dying*: 1) Denial and Isolation, 2) Anger, 3) Bargaining, and 4) Depression.⁴⁷ (*Appendix 3: Excerpts regarding Ethical Issues*)

The *de facto* denial of appropriately-timed administration of available COVID-19 Convalescent Plasma (available through the not-for-profit Blood Banks of America⁴⁸) in the aggregate has been relegated to the inconsequential, trivial, curiosity scrapheap for the last nine months. While the monoclonal antibodies of Eli Lilly⁴⁹ and Regeneron⁵⁰ and COVID-19 Convalescent Plasma are *all Passive Immunization* methodologies, as directed by Rear Admiral Hinton, administrations of the monoclonal antibodies have appropriately been designated to be given early in the individual's COVID-19 disease course and only in mildly symptomatic patients (no respiratory changes)^{42,43} BUT, COVID-19 Convalescent Plasma is to be given only in hospitalized patients. ^{16,17} In practice, those hospitalized are by definition more ill, later in the course of their COVID-19 disease, and more progressed in the severity of the SARS morbidity. (Withholding *Passive Imunization in the Treatment of COVID-19 (not prevention/vaccination)* is STUPID LOGIC and it is HURTING people!).

Obviously, this Letter to the Editor of *The New England Journal of Medicine* is <u>not</u> in the correct format, length, phraseology, nor length in the litany of references and appendices. I **hope**⁴⁷ and plead that the editors of *The New England Journal of Medicine* will publish this document to open a dialog about and expedite the appropriate <u>empiric</u> application of *Passive Immunization* in the <u>early treatment</u> of all persons (not just the privileged³⁹). While the vaccines (*Active Immunization*) will be distributed over the next six months to a year around the World, those who become infected with COVID-19 prior to vaccination will most assuredly benefit from *Passive Immunization*, *i.e.*: monoclonal antibodies or COVID-19 Convalescent Plasma.

As with my other submissions to Drs. Fauci and Hahn and the President of the United States over the last nine months, I will submit this to the U.S. Copyright Office of the Library of Congress to preserve for history the chronology of these pleas. ^{25,27,37} As I am the claimant of the previous submissions ^{25,27,37} and this present letter and all its attachments, I permit free and open reproduction of all by the Editors of *The New England Journal of Medicine* and any other publication in the World.

Respectfully yours,

Charles H. Andrus, M.D., F.A.C.S.
Professor of Surgery, Saint Louis University School of Medicine
Staff Surgeon, Surgical Service (112jc), John Cochran (St. Louis) VAMC,
Veterans Health Administration, U.S. Department of Veterans Affairs
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 https://web.archive.org/web/20200404213000/https://www.uscovidplasma.org/ (From April 4, 2020), While the nominal title of "National Expanded Access Treatment Protocol" implies that the USA government was directing the process—IT WAS NOT! In fact, the hyperlink: next to the National Expanded Access Treatment Protocol on the April 8, 2020 website version of Recommendations for Investigational COVID-19 Convalescent Plasma¹⁸ is representative of the FDA Disclaimer website disavowing any FDA responsibility regarding the National Expanded Access Treatment Protocol and misrepresenting itself:

Responding to the unprecedented challenge fighting coronavirus disease 2019 (COVID-19), the U.S. Government is supporting a national Expanded Treatment Protocol to collect and provide convalescent plasma to patients in need across the country. Plasma from recovered COVID-19 patients contains antibodies that may help fight the disease.

Working collaboratively with industry, academic, and government partners, Mayo Clinic will serve as the lead institution for the program, registering participating providers and potential patients who may benefit and qualify for this investigational treatment.

Subsequent iterations of the National Expanded Access Treatment Protocol: https://web.archive.org/web/20200407105003/https://www.uscovidplasma.org/ (From April 7, 2020)

https://www.uscovidplasma.org/ (From October 26, 2020).

24. U.S. Food & Drug Administration: Website Disclaimer. https://www.fda.gov/about-fda/website-policies/website-disclaimer

Website Disclaimer

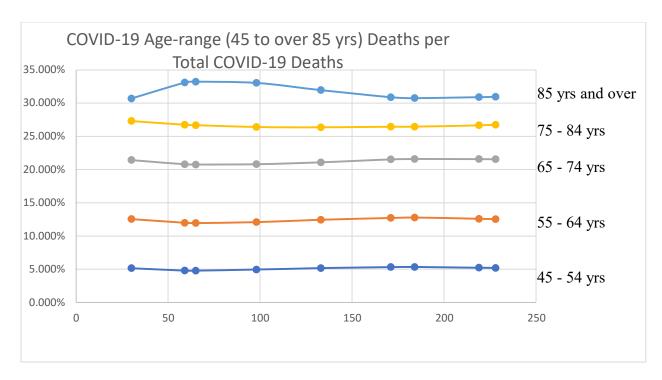
Our website has links to many other federal agencies, and, in a few cases, to private organizations, foreign governments and international organizations. You should be aware that:

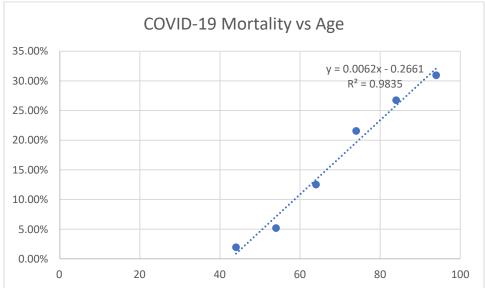
- This graphic notice, , means that you are leaving the U.S. Food and Drug Administration (FDA) site and entering a non-federal website.
- This external link provides additional information that is consistent with the intended purpose of the FDA site.
- The FDA cannot attest to the accuracy of information provided by this link.
- Linking to a non-federal site does not constitute an endorsement by FDA or any
 of its employees of the sponsors or the information and products presented on
 the site
- You will be subject to the destination site's privacy policy when you leave the FDA site.
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Serious Adverse Events. Key serious adverse events (SAE) related to the transfusion of convalescent plasma are reported in Table 2. Our report is not a comprehensive summary of all risks associated with hospitalization of COVID-19 but did assume that convalescent plasma potentially could cause life-threatening cardiac events and thrombotic events, so these were collected with an underlying assumption of attribution. Within four hours of completion of the COVID-19 convalescent plasma transfusion, 146 SAEs classified as transfusion reactions were reported (<1% of all transfusions). Of these SAEs, there were 83 nonmortality events reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction. Of the SAEs reported within four hours of plasma transfusion, there were 63 mortalities (0.3% of all transfusions) and 13 of these mortalities were judged as related (possibly, n=12; probably, n=1; definitely, n=0) to the transfusion of COVID-19 convalescent plasma. Within seven days of completion of the COVID-19 convalescent plasma transfusion, 1,136 other SAEs were reported. Of these SAEs, 87 thromboembolic or thrombotic events were reported, 406 sustained hypotensive events requiring intravenous pressor support were reported, and 643 patients suffered a cardiac

- event. Notably, the vast majority of the thromboembolic or thrombotic complications (n=55) and cardiac events (n=569) were judged to be unrelated to the plasma transfusion.
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The death rate to COVID-19 by age groups has been consistent by age range for the last nine months signifying that no organized treatment of the virus (not supportive therapy) has been employed in large enough numbers to make any significant difference. Mortality is a linear relationship versus age for anyone over 44 years-of-age: Mortality = [(0.0062% x age) - 0.2661%]; coefficient of determination ($\mathbb{R}^2 = 0.9835$).





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56.0 542 Appendix 1--Excerpts regarding Passive Immunization (1) copy.pdf

I. COVID-19 Convalescent Plasma

 U.S. Food & Drug Administration: Recommendations for investigational COVID-19 Convalescent Plasma. April 8, 2020. https://web.archive.org/web/20200408215026/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

a. April 8, 2020

FDA has issued <u>guidance</u> to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency.

The guidance provides recommendations on the following:

- pathways for use of investigational COVID-19 convalescent plasma
- patient eligibility
- collection of COVID-19 convalescent plasma, including donor eligibility and donor qualifications
- <u>labeling</u>, and
- record keeping

Because COVID-19 convalescent plasma has not yet been approved for use by FDA, it is regulated as an investigational product. A health care provider must participate in one of the pathways described below. FDA does not collect COVID-19 convalescent plasma or provide COVID-19 convalescent plasma. Health care providers or acute care facilities would instead obtain COVID-19 convalescent plasma from an FDA-registered blood establishment.

b. **Patient Eligibility**

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the <u>National Expanded Access Treatment Protocol</u>External Link Disclaimer. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,

- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
- lung infiltrates > 50% within 24 to 48 hours
- Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.
- U.S. Food & Drug Administration: Recommendations for investigational COVID-19 Convalescent Plasma. September 1, 2020 on the Wayback Machine of August 23, 2020. https://web.archive.org/web/20200901081726/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

a. August 23, 2020

FDA issued an <u>EUA for convalescent plasma</u> on August 23, 2020. Please check back for updates to this page in the near future.

FDA has issued <u>guidance</u> to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency.

The guidance provides recommendations on the following:

- pathways for use of investigational COVID-19 convalescent plasma
- patient eligibility
- <u>collection of COVID-19 convalescent plasma, including donor eligibility and donor qualifications</u>
- labeling, and
- record keeping

Because COVID-19 convalescent plasma has not yet been approved for use by FDA, it is regulated as an investigational product. A health care provider must participate in one of the pathways described below. FDA does not collect COVID-19 convalescent plasma or provide COVID-19 convalescent plasma. Health care providers or acute care facilities should instead obtain COVID-19 convalescent plasma from an FDA-registered blood establishment.

b. Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment ProtocolExternal Link Disclaimer. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.
- 3. U.S. Food & Drug Administration: Recommendations for investigational COVID-19 Convalescent Plasma. September 2, 2020. https://web.archive.org/web/20200902232530/https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
 - a. September 2, 2020

FDA issued an EUA for convalescent plasma on August 23, 2020.

FDA has issued a new <u>guidance</u> to provide recommendations to health care providers and investigators on the use of COVID-19 convalescent plasma under the EUA or investigational convalescent plasma under an IND during the public health emergency. The guidance also provides recommendations to blood establishments on collection. The guidance describes FDA's interim compliance and enforcement policy regarding the IND requirements for the use of investigational convalescent plasma to facilitate the availability of convalescent plasma to treat hospitalized patients with COVID-19. The guidance supersedes the guidance of the same title issued in April 2020 and updated in May 2020.

The guidance provides recommendations on the following:

- pathways for use of investigational convalescent plasma
- <u>collection of convalescent plasma</u>
- record keeping
- <u>compliance and enforcement policy regarding investigational</u> new drug requirements for use of convalescent plasma

Because convalescent plasma for the treatment of COVID-19 has not yet been approved for use by FDA, it is regulated as an investigational product. As such, its administration must be under the EUA or an IND. FDA does not collect convalescent plasma or provide convalescent plasma. Health care providers or acute care facilities should obtain convalescent plasma from an FDA registered or licensed blood establishment.

- b. Eligibility Criteria is missing from this version of the Recommendations for investigational COVID-19 Convalescent Plasma.
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 - a. November 16, 2020

FDA issued an EUA for convalescent plasma on August 23, 2020.

FDA has issued a new <u>guidance</u> to provide recommendations to health care providers and investigators on the use of COVID-19 convalescent plasma under the EUA or investigational convalescent plasma under an IND during the public health emergency. The guidance also provides recommendations to blood establishments on collection. The guidance describes FDA's interim compliance and enforcement policy regarding the IND requirements for the use of investigational convalescent plasma to facilitate the availability of convalescent plasma to treat hospitalized patients with COVID-19. The guidance supersedes the guidance of the same title issued in April 2020 and updated in May and September 2020.

The guidance provides recommendations on the following:

- pathways for use of investigational convalescent plasma
- collection of convalescent plasma
- record keeping
- compliance and enforcement policy regarding investigational new drug requirements for use of convalescent plasma

Because convalescent plasma for the treatment of COVID-19 has not yet been approved for use by FDA, it is regulated as an investigational product. As such, its administration must be under the EUA or an IND. FDA does not collect convalescent plasma or provide convalescent plasma. Health care providers or acute care facilities should obtain convalescent plasma from an FDA registered or licensed blood establishment.

- b. Eligibility Criteria is missing from this version of the Recommendations for investigational COVID-19 Convalescent Plasma.
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II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized bamlanivimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab to authorized distributors⁴, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;
- The bamlanivimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
- Bamlanivimab is not authorized for use in the following patient populations 5:
 - Adults or pediatric patients who are hospitalized due to COVID-19, or
 - Adults or pediatric patients who require oxygen therapy due to COVID19, or
 - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.
- Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
- The use of bamlanivimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.
- 6. FDA: FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB. https://www.fda.gov/media/143603/download

LIMITATIONS OF AUTHORIZED USE

• Bamlanivimab is not authorized for use in patients:

- o who are hospitalized due to COVID-19, OR
- o who require oxygen therapy due to COVID-19, OR
- o who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Bamlanivimab has been authorized by FDA for the emergency uses described above. Bamlanivimab is not FDA-approved for these uses.

Bamlanivimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bamlanivimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

This EUA is for the use of the unapproved product bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization [see Limitations of Authorized Use].

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) \geq 35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
 - o cardiovascular disease, OR
 - o hypertension, OR
 - o chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 17 years of age AND have
 - o BMI ≥85th percentile for their age and gender based on CDC growth charts,

https://www.cdc.gov/growthcharts/clinical_charts.htm, OR

- o sickle cell disease, OR
- o congenital or acquired heart disease, OR
- o neurodevelopmental disorders, for example, cerebral palsy,

OR

- o a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
- o asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Bamlanivimab must be administered by intravenous (IV) infusion.

Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion

reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

III. Regeneron monoclonal antibody cocktail: casirivimab and imdevimab

7. Rear Admiral Hinton DM, RN, MS, Chief Scientist, FDA: Letter to Regeneron Pharmaceuticals, Inc.: Letter of Authorization, EUA for casirivimab and imdevimab, November 21, 2020. https://www.fda.gov/media/143891/download

FDA: FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF CASIRIVIMAB AND IMDEVIMAB. https://www.fda.gov/media/143902/download

Casirivimab and imdevimab are not approved, but the U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products casirivimab and imdevimab to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID19 and/or hospitalization only for the duration of the declaration.

LIMITATIONS OF AUTHORIZED USE

- Casirivimab and imdevimab are not authorized for use in patients:
 - o who are hospitalized due to COVID-19, OR
 - o who require oxygen therapy due to COVID-19, OR
 - o who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS potentially related to casirivimab and imdevimab. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions.

⁵ Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

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57.0 543 Appendix 2: Remdesivir EUAs and NDA #NDA 214787

May 1, 2020: Initial Remdesivir EUA. Letter from RADM Hinton, FDA, to Ms Rhoades, Gilead Sciences, Inc. https://web.archive.org/web/20200501204823/https://www.fda.gov/media/137564/download

Page 2:

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized remdesivir will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Gilead will supply remdesivir to authorized distributors4, or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;
- The remdesivir covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as $SpO2 \le 94\%$ on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO);
- Remdesivir is administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider; and

August 28, 2020: Initial Remdesivir EUA. Letter from RADM Hinton, FDA, to Ms Rhoades, Gilead Sciences, Inc. https://web.archive.org/web/20200829175858/https://www.fda.gov/media/137564/download

Pages 1-2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury (remdesivir)³ for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)4, pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.

On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers has been revised to provide updated clinical trial results and supporting data.⁵

Pages 2-3:

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

¹ U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360 bbb-3.* February 4, 2020. ² U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).*

³ The May 1, 2020 EUA referred to the authorized drug as "remdesivir;" however, Gilead subsequently requested, and FDA concurred, that the Fact Sheets be altered to add references to remdesivir's trade name, "Veklury." "Veklury" is used in this August 28, 2020 reissued letter.

⁴ For purposes of the May 1, 2020 EUA, patients with severe disease were defined as patients with oxygen saturation ≤94% on room air or

⁴ For purposes of the May 1, 2020 EUA, patients with severe disease were defined as patients with oxygen saturation ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

⁵ Prior to this reisease and appropriate to the conditions of outbroighting. Gilead had requested and EDA had sensured with other phones to

⁵ Prior to this reissuance and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration

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• Distribution of the authorized Veklury will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA

Gilead will supply Veklury to authorized distributors⁷, or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;

- The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider; and
- The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

October 1, 2020: Remdesivir EUA. Letter for RADM Hinto to Ms Rhoades, Gilead Sciences, Inc. https://web.archive.org/web/20201002130204/https://www.fda.gov/media/137564/download

Pages 1-2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury (remdesivir)³ for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)⁴, pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.

On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the May 1, 2020, letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers was revised to provide updated clinical trial results and supporting data.⁵

CONTRARY TO REFERENCE #4 WHICH STATES: "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).", AS OF AUGUST 28, 2020, ... "expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."

On October 1, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the August 28, 2020, letter in its entirety with revisions incorporated to the scope and conditions of authorization designating Gilead Sciences, Inc. and its authorized distributors6 as the responsible parties for the distribution⁷ of Velkury.

Veklury has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the data from the randomized, double-blinded, placebo controlled trial conducted by NIAID (NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gileadsponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), it is reasonable to believe that Veklury may be effective and the known and potential benefits of Veklury outweigh the known and potential risks of the drug for the treatment of patients hospitalized with COVID-19.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Veklury for treatment of COVID-19, as described in the Scope of Authorization section of this reissued letter (Section II) and subject to the terms of this authorization.

I. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

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- The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an inpatient hospital setting via intravenous (IV) infusion by a healthcare provider; and
- The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

October 16, 2020: Remdesivir EUA. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. https://web.archive.org/web/20201017135559/https://www.fda.gov/media/137564/download

Pages 1-2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury (remdesivir)³ for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)⁴, pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.

On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the May 1, 2020, letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers was revised to provide updated clinical trial results and supporting data.⁵

CONTRARY TO REFERENCE #4 WHICH STATES: "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) <94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO),", AS OF AUGUST 28, 2020, ... "expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."

On October 1, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the August 28, 2020, letter in its entirety with revisions incorporated to the scope and conditions of authorization designating Gilead Sciences, Inc. and its authorized distributors⁶ as the responsible parties for the distribution⁷ of Velkury. FDA is reissuing the October 1, 2020, letter in its entirety with revisions to clarify that an alternate care site (ACS) meeting certain criteria is considered an "inpatient hospital setting" for the purposes of the scope of the EUA, and as such, is within the terms and conditions of FDA's authorization.

Veklury has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID

¹ U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020. ² U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).*

³ The May 1, 2020, EUA referred to the authorized drug as "remdesivir;" however, Gilead subsequently requested, and FDA concurred, that the Fact Sheets be altered to addreferences to remdesivir's trade name, "Veklury." "Veklury" is used in the August 28, 2020, reissued letter.

⁴ For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (FCMO).

or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

⁵ Prior to the reissuance of the EUA on August 28, 2020, and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance); (3) added hypersensitivity reaction and drug interaction information; (4) added safety information from randomized, clinical trials; (5) removed information related to the compassionate use program; and (6) added reference to remdesivir's trade name, Veklury.

⁶ "Authorized Distributor(s)" are identified by Gilead as an entity or entities allowed to distribute authorized Veklury.

⁷ Allocations of Veklury directed by the United States Government on or before September 30, 2020, remain valid and shall be distributed in collaboration with state or local government authorities, as needed.

⁸ No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

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(NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), it is reasonable to believe that Veklury may be effective and the known and potential benefits of Veklury outweigh the known and potential risks of the drug for the treatment of patients hospitalized with COVID-19.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Veklury for treatment of COVID-19, as described in the Scope of Authorization section of this reissued letter (Section II) and subject to the terms of this authorization.

dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance); (3) added hypersensitivity reaction and drug interaction information; (4) added safety information from randomized ,clinical trials; (5) removed information related to the compassionate use program; and (6) added reference to remdesivir's trade name, Veklury.

Page 3:

3. There is no adequate, approved, and available alternative to the emergency use of Veklury for the treatment of COVID-19. 8

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- The Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an inpatient hospital setting⁹ via intravenous (IV) infusion by a healthcare provider; and
- The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

October 22, 2020: Remdesivir EUA. Letter from RADM Hinton to Ms Rhoades, Gilead Sciences, Inc. https://www.fda.gov/media/137564/download

¹ U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020. ² U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).*

³ The May 1, 2020, EUA referred to the authorized drug as "remdesivir;" however, Gilead subsequently requested, and FDA concurred, that the Fact Sheets be altered to addreferences to remdesivir's trade name, "Veklury." "Veklury" is used in the August 28, 2020, reissued letter.

⁴ For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

⁵ Prior to the reissuance of the EUA on August 28, 2020, and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified

^{6 &}quot;Authorized Distributor(s)" are identified by Gilead as an entity or entities allowed to distribute authorized Veklury.

⁷ Allocations of Veklury directed by the United States Government on or before September 30, 2020, remain valid and shall be distributed in collaboration with state or local government authorities, as needed.

⁸ No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

⁹ Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.

¹⁰ The product labeled "investigational use" is authorized for use under this EUA; FDA is not requiring it to be relabeled given the immediate need for the product.

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Pages 1-2:

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury® (remdesivir) for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)³, pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. At that time, Veklury was an investigational drug and not approved for any indication.

On August 28, 2020, having concluded that revising this EUA was appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the May 1, 2020, letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers was revised to provide updated clinical trial results and supporting data.⁴

CONTRARY TO REFERENCE #3 WHICH STATES: "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).", AS OF AUGUST 28, 2020, ... "expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."

On October 1, 2020, having concluded that revising this EUA was appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the August 28, 2020, letter in its entirety with revisions incorporated to the scope and conditions of authorization designating Gilead Sciences, Inc. and its authorized distributors⁵ as the responsible parties for the distribution of Velkury. On October 16, 2020, FDA reissued the October 1, 2020, letter in its entirety with revisions to clarify that an alternate care site (ACS) meeting certain criteria was considered an "inpatient hospital setting" for the purposes of the scope of the EUA, and as such, was within the terms and conditions of FDA's authorization. On October 22, 2020, FDA approved NDA 214787 for Veklury (remdesivir), which is indicated for adults and pediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Under its approval, Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the October 16, 2020, letter in its entirety with revisions to remove uses previously authorized that are now the subject of the approved NDA 214787 for Veklury, and to continue authorizing Veklury for emergency use to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

Veklury has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the data from the randomized, double-blinded, placebo controlled trial conducted by NIAID (NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), it is reasonable to believe that Veklury may be effective and the known and potential benefits of Veklury outweigh the known and potential risks of the drug for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Veklury for treatment of COVID-19, as described in the Scope of Authorization section of this reissued letter (Section II) and subject to the terms of this authorization

¹ U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C.* § 360bbb-3. February 4, 2020. ² U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C.* § 360bbb-3, 85 FR 18250 (April 1, 2020).

³ For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

⁴ Prior to the reissuance of the EUA on August 28, 2020, and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance); (3) added hypersensitivity reaction and drug interaction information; (4) added safety information from randomized, clinical trials; (5) removed information

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related to the compassionate use program; and (6) added reference to remdesivir's trade name, Veklury.

⁵ "Authorized Distributor(s)" are identified by Gilead as an entity or entities allowed to distribute authorized Veklury.

CONTRARY TO REFERENCE #3 WHICH STATES: "For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).", AS OF AUGUST 28, 2020, ... "expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease."

Page 3:

- II. Scope of Authorization I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:
 - The Veklury covered by this authorization will be used only to treat suspected or laboratory-confirmed COVID-19 in hospitalized⁷ pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg administered via intravenous (IV) infusion by a healthcare provider; and
 - The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

⁶ No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

⁷ Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.

FDA's authorization includes remdesivir for injection manufactured and labeled prior to Gilead's reference to remdesivir's trade name, "Veklury", in product labeling.

PLEASE NOTE FOOTNOTE (7) ABOVE WHICH EXPANDS THE SITES OF INFUSION FROM "ACUTE INPATIENT HOSPITAL" TO "...ARE ADMITTED OR TRANSFERRED TO AN ALTERNATE CARE SITE (ACS) THAT IS CAPABLE OF PROVIDING ACUTE CARE THAT IS COMPARABLE TO GENERAL INPATIENT HOSPITAL CARE..."

October 22, 2020: Remdesivir NDA 214787. Letter from John Farley, MD, MPHto Ms Rhoades, Gilead Sciences, Inc. authorizing a New Drug Authorization Approval https://www.accessdata.fda.gov/drugsatfda docs/appletter/2020/214787Orig1s000ltr.pdf

NDA 214787

NDA APPROVAL

Gilead Sciences, Inc. Attention: Ashley Rhoades, MBS, RAC Manager, Regulatory Affairs 333 Lakeside Drive Foster City, CA 94404

Dear Ms. Rhoades:

Please refer to your new drug application (NDA) dated and received August 7, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VEKLURY (remdesivir) injection, 5 mg/mL; VEKLURY (remdesivir) for injection, 100 mg/vial.

This new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. **VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.**

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I am an Attending Physician and General Surgeon of the Surgical Service, St. Louis (John Cochran) VAMC, Veterans Health Administration, U.S. Department of Veterans Affairs. Recently, I had a patient in the hospital who became COVID-19 positive. The Saint Louis University General Surgery Residents of whom I oversee as the ACGME site-residency-director at my direction prescribed one dose of COVID-19 Convalescent Plasma (CCP) and a five-day-course of Remdesivir. While the patient received the CCP without question and after the first loading dose of Remdesivir, the pharmacy refused any additional doses as they were directed by the local Infectious Diseases team. The justification was:

Echevarria K: Remdesivir (Veklury) Criteria for Use, November 2020, VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives.

The *Inclusion Criteria* reads as follows which is <u>contrary to the EUAs of Rear Admiral Hinton, R.N., M.S.,</u> Chief Scientist, U.S. Food & Drug Administration from August 28, 2020 going forward to the present:

Inclusion Criteria

The following must be fulfilled in order to meet criteria from remdesivir
Hospitalized with **SEVERE** COVID-19 (room air oxygen saturation <94%, requiring supplemental.
oxygen or increase from baseline if on chronic oxygen or is requiring invasive or non-invasive ventilation or ECMO)***

Scanned version below:

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.		
Exclusion Criteria		
If the answer to ANY item below is met, then the patient should NOT receive remdesivir		
Treated for COVID-19 as an outpatient		
AST or ALT > 5 times the upper limit of normal		
Hospitalized patients but NOT requiring supplemental oxygen*		
Concomitant use of hydroxychloroquine or chloroquine		
Current eGFR < 30 mL/min**		
Inclusion Criteria		
The following must be fulfilled in order to meet criteria for remdesivir		
Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from		
baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***		
Supplemental Information		
Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving		
or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration of therapy has not been given		
*Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis		
**Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not		
recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks,		
especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance.		
***Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with		
corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19		
Described National Section & Wellin Education Described in Described in the Control of the Contr		
Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services 10P4P		
manager, and inquired penetry inquired them some process to the		

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Submission 09-12-2023 of BOOK1 Dear Mr. President -- COVID-19 and Where we went WRONG 544 Appendix 2B--RE_Remdesivir VA_R communications 12-15-2020 copy .pdf

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F**rom:** Charles.Andrus@va.go

To: Kelly.Echevarria@va.gov, Leslie.Compton@va.gov,

Cc: Jay.McDonald1@va.gov, Sarah.George@va.gov, candrus600@aol.com, charles.andrus@health.slu.edu, Jennifer.Zacher@va.gov, Richard.Stone2@va.gov,

Subject: RE: Remdesivir

Date: Tue, Dec 15, 2020 3:43 pm

Attachments:

12/15/2020

Kelly Echevarria, PharmD, BCPS, AQ-ID

Manager, National Clinical Pharmacy Program Manager

VA Pharmacy Benefits Management Services 10PAP

Dear Dr. Echevarria:

Thank you very much for your extensive response. Unfortunately, your reply e-mail has confirmed a significant contradiction between the VA Medical Advisory Panel and the Executive Summary of the NIH Therapeutic Management of Patients with COVID-19 (last updated, December 3, 2020) which you sent to me in your e-mail hyperlink: "here" (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/) in which in the executive summary it is stated:



Therapeutic Management of Patients with COVID-19

Last Updated: December 3, 2020

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

You also included as an attachment another hyperlink: Remdesivir Criteria for Use in which the following is stated as the only Inclusion Criteria for Remdesivir authorized by VACO:

12/17/2020 RE: Remdesivir

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CUNICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLÍNICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE

	DSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL PACILITY ACCORDING TO THE POLICY AND PROCEDURES OF BT COMMITTEE AND PHARMACY SERVICES.
The F	reduct information should be consulted for detailed prescribing information.
See t	he VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://voww.pbm.va.gov for further information.
Ex	clusion Criteria
If th	answer to ANY item below is met, then the patient should NOT receive remdesivir
	Treated for COVID-19 as an outpatient
	AST or ALT > 5 times the upper limit of normal
	Hospitalized patients but NOT requiring supplemental oxygen*
	Concomitant use of hydroxychloroquine or chloroquine
	Current eGFR < 30 mL/min**
Inc	clusion Criteria
The	following must be fulfilled in order to meet criteria for remdesivir
	Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from

This is absolutely contradictory to the NIH Executive Summary Above regarding the pathophysiology of COVID-19 and the therapeutic recommendations: "...it is anticipated that antiviral therapies would have greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19." Internally, though, what follows in the NIH Executive Summary is completely contradictory to the NIH's first paragraph. (Obviously, the NIH needs to deal with this.)

The VA Remdesivir Criteria for Use has now brought this to light. By this misinterpretation of the timing of administration of Remdesivir by the VA Pharmacy Panel (the FDA removed the severity criteria on August 28, 2020—the chronological history of the removal of the severity criteria is outlined in Rear Admiral Hinton's EUA on Remdesivir of October 22, 2020.), has condoned de facto discrimination against any Veteran patient who presents COVID-19 positive BUT without severe symptoms early in the course of his/her disease. Please provide this entire correspondence to the VA National Clinical Pharmacy Panel. The panel should probably decide whether this should also be provided to the Office of VA General Counsel and the VA Office of the Inspector General. Due to the seriousness of these contradictions and probably a condoned discrimatory practice by the VHA toward individual Veterans early-in-the-course of their COVID-19 disease, I will include Dr. Stone as he is the Executive in Charge, VHA, in this correspondence.

Sincerely,

Charles H. Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine

Attending General Surgeon, Unit II (SLU) General Surgery, Surgical Service (112-JC), St. Louis (John Cochran) VAMC

314-652-4100 ext 54463

Beeper 314-491-2417

Home phone: 314-455-9482

From: Echevarria, Kelly < Kelly. Echevarria@va.gov>

Sent: Tuesday, December 15, 2020 9:43 AM

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Submission 09-12-2023 of BOOK1 Dear Mr. President -- COVID-19 and Where we went WRONG

12/17/2020 RE: Remdesivir

Cc: McDonald, Jay R. (STL) < Jay.McDonald 1@va.gov>; George, Sarah L. (STL) < Sarah.George@va.gov>; candrus600@aol.com; challed and least the first the first control of the first the first control of the first control o

Subject: RE: Remdesivir

Good morning sir,

As you stated remdesivir was formally approved by the FDA as follows: indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

That being said, the VA National Formulary Committee reviews every new drug, including all data to determine the safest, most effective and most cost-effective way to use that product within the VA. Materials such as the drug monograph are developed for discussion and if deemed necessary to ensure safe and appropriate use, Criteria For Use are sometimes also developed that are evidence based but may not match the FDA indication exactly. This multi-disciplinary committee votes on formulary status and criteria after circulating draft documents to clinicians in the field for comments and suggestions.

In the case of remdesivir, the data is inconsistent, with ACTT-1 showing benefit primarily in the subpopulation of patients requiring supplemental oxygen at baseline. Patients hospitalized but not requiring oxygen, and those on mechanical ventilation or ECMO did not derive a significant benefit from remdesivir in this setting. In addition, when the data was looked at by separating mild-moderate disease from severe, only the severe group had a significant benefit in terms of outcome.

The moderate SIMPLE trials from Gilead was open label and compared 5 vs. 10 days of remdesivir vs. no therapy and although 5 days was associated with clinical benefit (more likely to have improved clinical status at day 11) but the 10 day group did not, and confidence intervals were wide. The severe SIMPLE trial is largely uninterpretable for safety or efficacy as there was no standard of care arm.

The NIH COVID-19 guidelines generally do not recommend remdesivir for patients not requiring oxygen or for those ill enough to require invasive mechanical ventilation or ECMO, although there may be cases where it is appropriate, such as very high risk patients or those rapidly progressing. Their treatment algorithm can be found here. The WHO doesn't recommend remdesivir at all given the somewhat conflicting data and the SOLIDARITY trial not showing evidence of benefit.

The VA Criteria for use and drug monograph are below and were approved after field comments, and approval by the VPE/MAP national formulary committee. Essentially anyone requiring oxygen, with a room air saturation < 94% or other indicators of severe disease is eligible provided they do not have exclusions. There may be situations, which can be adjudicated on a case by case basis where the benefit may be felt to outweigh the risks by the ordering provider, but as a general rule, given the lack of benefit in the subpopulation not requiring supplemental oxygen, it isn't routinely recommended. The Committee voted to add remdesivir to formulary as a Prior Authorization product at the facility level with the criteria for use below.

Please let me know if you have any additional questions or comments that I can address. A request for a change of CFU or formulary status can be taken through the local facility P&T to the VISN P&T and then to the National Formulary Committee if desired.

Remdesivir drug monograph

Remdesivir Criteria for Use

From: Andrus, Charles H. (STL) < Charles.Andrus@va.gov>

Sent: Monday, December 14, 2020 2:28 PM

To: Compton, Leslie R. (STL) < Leslie.Compton@va.gov>

 $\textbf{Cc:} \ \ \textbf{McDonald, Jay} \ \ \textbf{R.} \ \ (\textbf{STL}) < \underline{\textbf{Jay.McDonald1@va.gov}} > ; \ \textbf{George, Sarah} \ \ \textbf{L.} \ \ (\textbf{STL}) < \underline{\textbf{Sarah.George@va.gov}} > ; \ \textbf{Echevarria, Kelly} < \underline{\textbf{Kelly.Echevarria@va.gov}} > ; \ \textbf{Andrus, McDonald1.}$

Charles H. (STL) < Charles. Andrus@va.gov>; candrus600@aol.com; charles. andrus@health.slu.edu

Subject: RE: Remdesivir

12/14/2020

Dear Drs. Compton, McDonald, George, and Echevarria:

Attached are excerpts from the FDA EUAs regarding Remdesivir to the present by Rear Admiral Hinton, R.N., M.S., Chief Scientist, U.S. Food & Drug Administration. I am forwarding the attachment to all of you to document what is in the August 28, 2020- EUA for Remdesivir by the FDA: "...FDA is reissuing the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease." With the This submission is NOT for financial gain but for educational purposes only for ALL the American people

12/17/2020

RE: Remdesivir

issuing of approval on October 22, 2020 of the NDA 214787 for remdesivir, John Farley, MD, MPH, Director, Office of Infectious Disease Center of Directory valuation and Research, U.S. FDA stated: "This new drug application provides for the use of VEKLURY (remdesivir) injection and VEKLURY (remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighting at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care." Dr. Farley did not reinstate nor insert any of the previous "severity criteria" that had been removed by Rear Admiral Hinton on August 28, 2020.

Sincerely,

Charles H. Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine

Staff Surgeon, Chief, Unit II General Surgery, Surgical Service, St. Louis (John Cochran) VAMC (112jc), 915 N Grand Blvd, St. Louis, MO

Office: 314-652-4100 ext: 54463

Beeper: 314-491-2417

From: Compton, Leslie R. (STL) < Leslie.Compton@va.gov >

Sent: Thursday, December 10, 2020 2:34 PM

To: Andrus, Charles H. (STL) < Charles.Andrus@va.gov>

Subject: Remdesivir

Good afternoon, Dr. Andrus. I got your voicemail and wanted to follow up. While Veklury (remdesivir) was approved by the FDA, we still have to comply with the VA National Formulary, which indicates criteria for use must be met for remdesivir use. I have attached the criteria for use if you are interested.

Thank you

Leslie Compton, PharmD

Pharmacy Operations Manager

VA St. Louis Health Care System

John Cochran Division

Phone: 314-652-4100 ext 56338

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59.0 545 Appendix 2C--VACO Remdesivir (VEKLURY) Oriteria

Remdesivir (VEKLURY) CF for Use November 2020 (1) copy.pdf

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria
If the answer to ANY item below is met, then the patient should NOT receive remdesivir
Treated for COVID-19 as an outpatient
AST or ALT > 5 times the upper limit of normal
Hospitalized patients but NOT requiring supplemental oxygen*
Concomitant use of hydroxychloroguine or chloroguine
Current eGFR < 30 mL/min**
Inclusion Criteria
The following must be fulfilled in order to meet criteria for remdesivir
Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from
baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
Supplemental Information is the first of the last of t
Recommended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving
or who remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration
of therapy has not been given
*Use in hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be adjudicated on a case by case basis
**Patients with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not
recommended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks
especially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on local guidance.
***Remdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with
corticosteroids in patients who have recently been intubated, according to the NIH Treatment Guidelines for COVID-19
Prepared: November 2020. Contact: Kelly Echevarria, PharmD, BCPS, AQ-ID, BCIDP, National Clinical Pharmacy Program

Manager, VA Pharmacy Benefits Management Services 10P4P

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60.0 546 Appendix 3: Ethical Issues

Kozlov M: Two Washington U. doctors lead national effort to study new COVID-19 treatment.
 St. Louis Post-Dispatch, Aug 12, 2020.
 <u>Https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article_cce0f56-4493-5a26-8601-45e35d364b2d.html

</u>

Since April, the Trump administration has set aside <u>more than \$300 million</u> to collect plasma and, with the Mayo Clinic, launch an experimental drug program, serving high-risk patients with few other treatment options. More than 60,000 have received plasma.

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" said Grossman, who is also director of transfusion medicine at Barnes-Jewish Hospital.

(This coercive statement is contrary to the policies and directions of the Institutional Review Boards (IRB) which are overseen and report directly to the U.S. Food & Drug Administration: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/institutional-review-boards-irbs-and-protection-human-subjects-clinical-trials)

 The National Academies of Sciences, Engineering and Medicine: Integrating clinical research into epidemic response: The Ebola Experience, Eds: Keusch G, McAdam K, Cuff PA, Mancher M, Busta ER. Washington, DC: The National Academies Press, 2017. https://www.nap.edu/download/24739

Page 40-41:

Expanded Access Although providing experimental therapies in the context of a clinical trial is the ideal way to monitor and minimize risks of unproven agents while maximizing the scientific information gained, in some circumstances it is appropriate to administer unproven agents outside of an approved clinical trial. This is called an expanded access exemption or "compassionate use." In the United States, a number of conditions must be met in order for a patient to be granted access to a drug under expanded access: (1) there is no comparable or satisfactory therapy available, (2) the probable risk from the investigational product is not greater than the probable risk from the disease, and (3) providing the investigational product will not interfere with the conduct of clinical trials (FDA, 2016). The foreign aid workers, like Brantley and Writebol, received experimental therapies under an expanded access framework. In October 2014, the WHO working group report referred to compassionate use of investigational products as justifiable as long as data are collected and shared (WHO, 2015). However, most of the examples of expanded access provided were cases of foreign health workers who were evacuated from West Africa to the United States or Europe in order to ensure that they received optimal supportive care, and who, in desperation, were also offered whatever experimental intervention was available—and more than one if available (Enserink, 2014b). In this context, it would have been extremely difficult to attribute either beneficial or detrimental outcomes to any one of these investigational agents. The use of investigational agents under expanded access in these situations did not contribute to the knowledge base, but they did serve to initiate rumors that there was a cure for the foreigners that was not being made available to Africans. The belief that investigational agents in the very early stages of development were likely to be highly effective

furthered the view that randomized controlled trials were unethical. For example, Caplan et al. concluded that because "all available agents have been variously deployed against infected persons treated in the United States and Europe, the case for randomization to placebo in West Africa is morally suspect" (Caplan et al., 2015, p. 6).

Page 42 - 43:

Others argued that expanded access should be avoided because its "use exposes many patients to investigational interventions, often undermines fair access to experimental agents, compromises the collection of robust data to determine the safety and efficacy of interventions, and consumes scarce resources for uncertain clinical benefits" (Rid and Emanuel, 2014, p. 1844). Additionally, given the limited supply of experimental Ebola treatments and vaccines at the time, randomized trials may actually have been the most equitable way to distribute these products (Largent, 2016; Rettner, 2014). The strongest argument for providing expanded access to unproven therapies during the Ebola epidemic is that the high lethality of the disease tipped the ethical scales in favor of providing interventions that could be helpful, however remote that prospect of benefit may have been and even given the potential for harm. This argument springs from the principle of beneficence—the notion that medical care providers should seek to help patients. Yet even under such conditions, the social costs of providing expanded access merit consideration. Specifically, under circumstances like the Ebola epidemic, the principle of beneficence supports providing products under an expanded access exception when the following conditions are met (Darrow et al., 2015; FDA, 2016):

- A sufficient amount of the product is available after supplying the needs of clinical trials.
- Providing expanded access would not preclude or delay the initiation of more conclusive investigations of the intervention in properly designed studies. This could occur, for example, if the availability of investigational products off protocol depleted the supply of individuals willing to enroll in studies that could yield generalizable knowledge about the product's safety and efficacy.
- Existing evidence does not suggest such an unfavorable risk-benefit balance that the product would not even "make the cut" for inclusion in clinical trials.

Conclusion 2-1 The use of unproven experimental therapies— especially those in the early phases of drug development—under an expanded access exemption to patients regardless of nationality or where they are located, not only fails to provide information on safety or efficacy, but also creates inequities with the larger affected population during an epidemic. Such uses can promote the public misconcep-

tion that a safe and effective treatment exists and may generate mistrust of researchers and research efforts that will make it more difficult to launch clinical trials when additional interventions become available.

PLANNING CLINICAL TRIALS

Given the urgency of the situation, the August 2014 WHO ethics panel concluded that there was an "ethical imperative to offer the available experimental interventions that have shown promising results," noting that the "only way of obtaining evidence on the safety and efficacy of any intervention in Ebola virus disease is during an outbreak" (WHO, 2014a, p. 4). The panel stated that compassionate use is "justified as an exceptional emergency measure" but said that it should not "preclude or delay the initiation of more conclusive investigations of the intervention(s) in properly designed clinical studies" (WHO, 2014a, pp. 5–6). The panel identified a number of conditions for the use of investigational interventions (WHO, 2014a):

- The investigations should not divert attention or resources from public health measures.
- Ethical criteria should guide the use of such interventions.
- The use of the interventions should be based on the best possible assessment of risk and benefit.
- The interventions should have been demonstrated to be safe and effective in animal models, in particular in nonhuman primates.
- Expanded access for individual use should be employed only with a shared understanding of the criteria for such exceptions, and it should not preclude or delay high-quality clinical investigations.
- The uncertainty about the safety and efficacy of the interventions should be acknowledged and communicated to all stakeholders to avoid unfounded expectations.
- Investigational therapies should be administered in concert with necessary supportive treatment, management of side effects, and monitoring the progress of treatment.
- The data generated from the use of investigational therapies should be systematically collected and shared.
- The decision to use investigational therapies should take into consideration the available standard of care and feasibility in the setting.

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- ...Even with preliminary evidence, a drug in development with limited or no human safety and efficacy data would be very unlikely to gain regulatory approval on the basis of data generated during the outbreak and in time to be deployed during the same outbreak. Unless the data were especially promising, the likely best case scenario for a new drug or vaccine would be provisional approval for use in clinical trials or possibly for expanded access to high-risk groups, but not approval for the general population. Even with a limited expanded access approval, manufacturers would have to ramp up rapidly to make the product available before the epidemic waned.
- 3. World Health Organization (WHO): 2015a. Compassionate use of experimental treatments for Ebola virus disease: Outcomes in 14 patients admitted from August to November, 2014. https://www.who.int/medicines/ebola-treatment/outcomes_experimental_therapies/en/

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61.0 0.1 Index Appendix F

01 Letter to the President

02 Index

03 Paper: Early Passive Immunization and Antiviral in the Treatment of COVID-19

04 Table 1 US edit 1 owid-covid-data (5) 5-30-2021.xlsx

05 Graph 1—2020-2021 US COVID-19 Daily New Cases and Deaths.pptx

06 Graph 2—U.S. spikes and decreases of daily deaths.pptx

07 Table 2 Confirmed COVID-19 U.S. Cases.xlsx

08 Graph 3—U.S. spikes and decreases of daily deaths.pptx

09 Table 3 U.S. Deaths Due to COVID-19.xlsx

10 COVID-19 age-range deaths

Appendix A—abbr Time Crucial Independent Variable COVID-19 Pandemic TXu002199029

202 Time Crucial Independent Variable COVID-19 Pandemic 06 7-2020 copy.pdf

212 Table 1 Demographics (1) copy.pdf

213 Table 2 Confirmed COVID-19 Cases copy.pdf

214 Table 3 Deaths Due to COVID-19 copy.pdf

215 Graphs 1 2 3 copy.pdf

216 Graph 4 Hospital Numbers copy.pdf

Appendix B—abbr Mayo Clinic Safety Update Should be Completed Phase I Trial TXu2214049

321 Classify Mayo Safety Update as Completed Phase 1 Trial of

COVID-19 Convalescent Plasma (1) copy.pdf

322 Table I – Listing of USA Trials on NIHClinicalTrials 7-6-2020 (1) copy.pdf

323 Table II – Mayo Clinic study morbidity and odds of dying copy.pdf

Appendix C – Copy of letters sent to 537 Congressional offices August 2020

01 Dear Members of Congress and President Trump 8 23 2020

02 Dear Members of the US House of Representatives 8 28 2020

Appendix D Abbr Mr President PLEASE COVID-19 Covalescent Plasma TXu002232947

431 Dear Mr PresidentCOVID-19 Convalescent Plasma NOW 11-17-2020 (1) copy.pdf

432 Table I Excerpts from WH briefings etc 11-14-2020 copy.pdf

433 Table II Availability of Passive Immunization 11-15-2020 copy.pdf

434 FDA recommendations 11 14 2020 copy.pdf

Appendix E—Correspondence with VA and NEJM Dec 2020

505.1 Remdesivir VA corr from Nov 2020 to 12 24 2020.pdf

510 12 20 2020 response to the VHA USH.pdf

541 Letter to NEJM editor 12 13 2020 (1) copy.pdf

542 Appendix 1—Excerpts regarding Passive Immunization (1) copy.pdf

543 Appendix 2A—Remdesivir ERAs and NDA no 214787 (1) copy.pdf

544 Appendix 2B—RE_Remdesivir VA communicationjs 12-15-2020 copy.pdf

545 Appendix 2C—VACO Remdesivir (VEKLURY) Criteria for Use November 2020(1) copy.pdf 546 Appendix 3—Ethical Issues (1) copy.pdf

Appendix F—Letter to Dr. Birx 2-1-2021 *et. al.* with attachments indexed below 101 E-mail to Dr. Birx 2-1-2021 (1) copy.pdf 102 COVID-19 age-range deaths 2-1-2021 copy.pdf

Can be found in Appendix A

202 Time Crucial Independent Variable COVID-19 Pandemic 06 7-2020 copy.pdf

212 Table 1 Demographics (1) copy.pdf

213 Table 2 Confirmed COVID-19 Cases copy.pdf

214 Table 3 Deaths Due to COVID-19 copy.pdf

215 Graphs 1 2 3 copy.pdf

216 Graph 4 Hospital Numbers copy.pdf

Can be found in Appendix B

321 Classify Mayo Safety Update as Completed Phase 1 Trial of COVID-19 Convalescent Plasma (1) copy.pdf

322 Table I – Listing of USA Trials on NIHClinicalTrials 7-6-2020 (1) copy.pdf

323 Table II – Mayo Clinic study morbidity and odds of dying copy.pdf

Can be found in Appendix D

431 Dear Mr PresidentCOVID-19 Convalescent Plasma NOW 11-17-2020 (1) copy.pdf

432 Table I Excerpts from WH briefings etc 11-14-2020 copy.pdf

433 Table II Availability of Passive Immunization 11-15-2020 copy.pdf

434 FDA recommendations 11_14_2020 copy.pdf

Can be found in Appendix E

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541 Letter to NEJM editor 12_13_2020 (1) copy.pdf

542 Appendix 1—Excerpts regarding Passive Immunization (1) copy.pdf

543 Appendix 2A—Remdesivir ERAs and NDA no 214787 (1) copy.pdf

544 Appendix 2B—RE Remdesivir VA communication is 12-15-2020 copy.pdf

545 Appendix 2C—VACO Remdesivir (VEKLURY) Criteria for Use November 2020(1) copy.pdf

546 Appendix 3—Ethical Issues (1) copy.pdf

Appendix G—NIH and FDA responses including establish NIAID Case #12276 6-10-2020 NIH and FDA responses including 6-6-2020 re NIAID Case #12276.pdf

Timeline Bibliography 2021-06-04 Master References

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62.0 102 E-mail to Dr. Birx 2-1-2021 (1) copy.pdf

Andrus, Charles H. (STL)

From: Andrus, Charles H. (STL)

Sent: Monday, February 1, 2021 12:45 PM

To: emg5@cdc.gov

Cc: Anthony.Fauci@nih.hhs.gov; Francis.Collins@nih.hhs.gov; Janet.Woodcock@fda.hhs.gov;

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@aol.com; Charles Andrus

Subject: Thank you Dr. Birx for your discussion on Face the Nation of 1/24/2021

Attachments: COVID-19 age-range deaths 2-1-2021.pdf

February 1, 2021

Dear Dr. Birx:

On March 24, 2020, while there was much discussion and debate about COVID-19 convalescent plasma and the possible development of monoclonal antibodies against COVID-19, U.S. Medicine and the Government failed to explain to the American public the differences and individual utilities of *Active Immunization* (vaccines to stimulate patient antibody production) and *Passive Immunization* (provision of convalescent plasmas, convalescence sera, and immunoglobins from other species providing already formed antibodies (IgM, IgG, and IgA) against the virus in COVID-19 immunologically naïve patients immediately within 72 hours of diagnosis (testing positive).

In your interview with Margaret Brennan, you stated the following:

DR. BIRX: Well, what I do know and what was reassuring to me all along is I knew this would be studied. I knew that the emails, the reports that I wrote, the request to expand testing, the **how to improve therapeutics**, all of that, all of that would eventually come to light. Maybe not in my lifetime.

Last summer you stated that we should collect 500,000 units of convalescent plasma to prepare for the spike in the Fall –well, we as a nation didn't do that. In fact, as you are a Clinical Immunologist, you are very well aware of *Passive Immunization* in the <u>initial early treatment (<72 hours)</u> with the contraction of or exposure to a disease without any true alternate therapy as soon as possible (<72 hours) [e.g.: rabies, hydrops fetalis (Rhogam within 72 hours to an Rh negative mother at delivery of the <u>prior pregnancy</u>, snake bites, etc]. In fact, to withhold *Passive Immunization* (RhoGAM) from a newly delivered Rh negative mother is considered malpractice. By semantics and legal obfuscation, over the course of the last 10 months, the American public has been led down the rabbit hole by the Medical and Research community, the "Industry", and the Federal Government by <u>not officially providing any timely-appropriate immunotherapy</u> in the treatment of COVID-19 positivity with *Passive Immunization* until recently:

1. In March 2020, the FDA declared COVID-19 Convalescent Plasma *Investigational* instead of a *Biosimilar* biologic;

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- 2. On March 24, 2020 the FDA outlined *Eligibility Criteria* in the <u>late treatment of severe COVID-19</u> <u>disease</u> with COVID-19 Convalescent Plasma (at deaths door when the viremia is not the cause of death but rather the SARS pathophysiology) justifying this choice of late administration as the <u>US did not have enough</u> recovered convalescent patients (>14 days);
- 3. In early April 2020, the Mayo Clinic with the FDA offered COVID-19 Convalescent Plasma in the Expand Access protocol Convalescent Plasma COVID-19 (Coronavirus) Treatment (uscovidplasma.org) using the atdeaths-door *Eligibility Criteria* ("expanded access" is really "compassionate use"—so, therefore, any resultant data cannot officially be used for completion of a Phase I Clinical Trial). Over 94,000 units of COVID-19 plasma were given AT THE THERAPEUTICALLY WRONG TIME only to severely-effected patients with SARS pneumonitis or MSOF.
- 4. Throughout the last 11 months, the DHHS through the FDA and NIH has equated Safety Trials (Phase I trials) with Efficacy Trials (Phase II/III) so that there are no "Completed" Phase I (safety) trials with regards to COVID-19 biologics. Who should explain to the American people if the NIH plans on evading ad infinitum the "Right to Try" Law PL-115-176? Has not a bad precedent been set by not declaring a "completed" Phase I Trial with regards to COVID-19 Convalescent Plasma? Will any NIH protocol or FDA new drug/biologic Phase II/III trial and in any future research not be required to abide by the "Right to Try" Law, PL-115-176? In essence, the FDA and NIH are in violation of or at least in violation of the intent of federal law PL-115-176 which requires a "Completed" Phase I Trial only for application of PL-115-176. Forcing patients to participate in Placebo-controlled Phase II/ III Trials is coercion which is prohibited by every IRB in the nation. On August 12, 2020 in the St. Louis Post-Dispatch, the following quote involving one of the FDA-Mayo Clinic's named investigators was documented:

But the program has also had an unintended consequence: Patients aren't signing up for controlled trials, which compare outcomes for patients randomly assigned to receive the treatment with those who receive a placebo.

"If you have a 50% chance of getting either the stuff or nothing, which would you choose?" https://www.stltoday.com/lifestyles/health-med-fit/coronavirus/two-washington-u-doctors-lead-national-effort-to-study-new-covid-19-treatment/article ccec0f56-4493-5a26-8601-45e35d364b2d.html

No IRB, worth their salt, should ever approve of such a concept of coercion in any Clinical Trial; and the FDA should not only shut down any Clinical Trial with such flagrant coercion but also censure, if not shut down, any IRB that permitted such coercion.

5. All summer, the FDA kept announcing they were close to releasing an EUA regarding COVID-19 Convalescent Plasma. President Trump went to the American Red Cross at the end of July confirming the need in his mind and that of the President's COVID-19 Taskforce for COVID-19 Convalescent Plasma. The announcement of the EUA was delayed until it would be announced on Sunday, August 23, 2020, by President Trump on the eve of the Republican National Convention. The next day, the NIH COVID-19 Guidelines Panel condemned the EUA for lacking scientific rigorous analysis (being based on Expanded Access/Compassionate Use protocol data from the FDA/Mayo clinic study). In the most-recent guidelines of the NIH COVID-19 Guideline Panel of January 14, 2021, the NIH COVID-19 Guidelines Panel is now hedging its bets by hiding under "Convalescent Plasma" Last Update October 9, 2020:

Rationale for Recommendation

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Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

(While the Mayo Clinic's Expanded Access Program (EAP) did not have an official "untreated control arm" since it was *Compassionate Use* only, the Mayo Clinic's EAP Safety Update in June 2020 of 20,000 patients actually included a total of 21,987 infused patients with 1,987 patients not completing the post-infusion 7-day period and 8,130 being untreated. When one back-calculates varying the possible mortality rate in this untreated group, a mortality rate of 8.7% or greater in the "control group" would have been statistically significant with less than a 0.05% confidence level. *But, unfortunately, the Mayo Clinic's Expanded Access Program* did not even qualify as a "Completed Phase I Study" by the "purism" semantics of the NIH. Dr. Birx, the FDA has final statutory say over all new drugs and biologics, <u>NOT</u> the NIH.)

- 6. The Chief Scientist of the FDA, Rear Admiral Hinton, began the FDA removing the severity criteria by removing completely the *Eligibility Criteria* regarding Remdesivir on August 28, 2020 (the VA Central Office pharmacy formulary panel was still insisting on the severity *Eligibilty Criteria* as the only criteria for those eligible for Remdesivir in November 2020--three months after it was rescinded by Rear Admiral Hinton). Veklury (remdesivir) EUA Letter of Approval, reissued 10/22/2020 (fda.gov)
- 7. On September 2, 2020, the FDA removed completely without public awareness the severe disease *Eligibility Criteria* for COVID-19 Convalescent Plasma. Many institutions are still applying the severe disease *Eligibility Criteria* to this day--thus refusing patients COVID-19 Convalescent Plasma treatment when they first become COVID-19 positive and present to the local ER—including recently a newly positive COVID-19 patient with a 104° fever and uncontrollable cough that I personally know was refused by a University Hospital ER physician in a large University Hospital being told that only admitted patients to the ICU would be considered for therapy. (i.e.: The FDA's complete removal of the *Eligibility Criteria* after September 2, 2020 can be demonstrated by viewing an example of the U.S. Food & Drug Administration's website: *Recommendations for Investigational COVID-19 Convalescent Plasma* by comparing this most recent URL: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma by copying and pasting the URL into the Internet Archive (Wayback Machine) and displaying a URL before September 2, 2020 in which the severe disease *Eligibility Criteria* was outlined from April 2020 to September 2, 2020: Recommendations for Investigational COVID-19 Convalescent Plasma | FDA (archive.org):

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol External Link Disclaimer. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),

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- respiratory frequency ≥ 30/min,
- blood oxygen saturation ≤ 93%,
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
- lung infiltrates > 50% within 24 to 48 hours
- O Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.
- 8. Before the EUAs were issued by Rear Admiral Hinton regarding the Regeneron monoclonal cocktail (casirivimib and imdevimab) and Eli Lilly monoclonal antibody bamlanivimib, on October 26, 2020 Eli Lilly asked the FDA to exclude the use of their monoclonal antibody in patients with any signs of severity of associated illness parameters such as any new requirement of oxygen supplementation in any non-COPD patient or increase in amount of oxygen supplementation in COPD patients.
- Rear Admiral Hinton issued EUAs for Eli Lilly's bamlanivimib
 (https://www.fda.gov/media/143602/download) on November 10, 2020 and for Regeneron's casirivimib and imdevimab on November 21, 2020
 (https://www.fda.gov/media/143891/download). Both EUAs state the following (I will use the Regeneron's monoclonal cocktail as the example as President Trump had received this "experimental" cocktail in early October 2020 prior to the issuing of these EUAs):

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized casirivimab and imdevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply casirivimab and imdevimab to authorized distributor(s)4, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;
- The casirivimab and imdevimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization;
- Casirivimab and imdevimab may only be administered together;
- Casirivimab and imdevimab is not authorized for use in the following patient populations 5:
 - Adults or pediatric patients who are hospitalized due to COVID-19, or
 - Adults or pediatric patients who require oxygen therapy due to COVID19, or
 - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.
- Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
- The use of casirivimab and imdevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.
- 10. On November 24, 2020, in *NEJM* published: Simonovich VA, *et al*: A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia (nejm.org) which is an outstanding, well-thought-out prospective randomized trial using the discontinued/withdrawn severely-ill COVID-19 patient *Eligibility Criteria* in which all COVID-19 Convalescent Plasma was given only in patients with severe COVID-19 SARS pneumonitis. Unfortunately, the authors failed to mention in their paper's <u>abstract conclusion</u> that the

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outcome of the study was based on patients given COVID-19 Convalescent Plasma with only severe SARS pneumonitis—following the previously omitted (September 2, 2020) severe patient *Eligibility Criteria* in which *Passive Immunization* was administered at the WRONG TIME—that is at deaths-door instead of within 72-hours of COVID-19 positivity!:

CONCLUSIONS

No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. (PlasmAr ClinicalTrials.gov number, NCT04383535. opens in new tab.)

11. I wrote a Letter to the Editors of *The New England Journal of Medicine (NEJM)* regarding Simonovich VA, *et al* and included those I could access with regards to e-mails in the DHHS, the VA, and Saint Louis University SOM as I am a Professor of Surgery and the General Surgery Residency site director at the St. Louis (John Cochran) VAMC. I never got a response back from the *NEJM* but on January 6, 2021, the landmark article by Libster R, *et al*: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) demonstrated a statistically significant decrease in mortality and severity of illness in a specific age group (the elderly) when COVID-19 Convalescent Plasma was given within 72 hours (AT THE RIGHT TIME) of detection of COVID-19 positivity. As is stated in the conclusion of the abstract in this article:

CONCLUSIONS

Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19. (Funded by the Bill and Melinda Gates Foundation and the Fundación INFANT Pandemic Fund; Dirección de Sangre y Medicina Transfusional del Ministerio de Salud number, PAEPCC19, Plataforma de Registro Informatizado de Investigaciones en Salud number, 1421, and ClinicalTrials.gov number, NCT04479163.)

One of my fellow Attending Surgeons at the VA came to my office after my e-mail cover letter to my Letter to the Editors to *NEJM* and stated that I had every right under the First Amendment to communicate whatever I wished but I was just making a fool of myself as there were much smarter people than me involved in setting standards for COVID-19 therapy. The next night, I got a call from an administrator at Saint Louis University SOM (SLUSOM) stating I was only allowed to speak about COVID-19 Convalescent Plasma with other faculty members of SLUSOM and the physicians, nurses, and other healthcare personnel at the local VA--St. Louis (John Cochran) VAMC and to STOP calling Washington DC. He then asked me unknowingly why I had included e-mails to Harvard. I responded that the e-mail concerned my cover letter regarding my letter to the Editors of *The New England Journal of Medicine*. He responded: Oh...—speak only with those in the local VA and Saint Louis University.

[Please note I attached a slide of mortality due to COVID-19 by age range between March and November 2020. First, the mortality percentages by age range have not changed over those 9 months suggesting the USA has not diminished the death rate by any therapy employed so far in any age group over 40 years of age. Second, you will note, the mortality rate from 40 to 90 years increases by 0.67% per year: y = 0.0067x - 0.2647, $R^2 = 0.9676$; and, below age 40, the mortality rate increases only by 0.04% per year to maximally 0.12%/year: y = 0.0004x - 0.0023, R = 0.7987. Once again, as the mortality rates in all range groups over the age of 40 have not changed over the last 10 months per age groups, the late administration of *Passive Immunization* to the majority of the hundred thousand patients that received COVID-19 Convalescent Plasma was given at the WRONG TIME using the now rescinded FDA patient *Eligibility Criteria*--such administration at the WRONG TIME did not make a substantial impact. What this also implies is that sending the children and young adults back to in-

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school-learning will be relatively safe for the children. The mortality rate of 0.04% increase per year per age group in children is markedly less when compared with adults over age 40 years with an increase in mortality rate of 0.67% per year per age group which is 16x higher in adults than in children. This presents the possibility of the USA generating a vector repository in our children who could then transmit COVID-19 to their parents, grandparents, and other adults who have a higher risk of severity of disease and death.]

- 12. The NEJM landmark article of January 6, 2021 by Libster R, et al: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org) was overshadowed by the events that occurred later in the day in Washington D.C. Ironically, on January 14, 2021, USA Today ran an article: Rodriguez A: US officials urge Americans to ask their doctors about monoclonal antibodies for COVID. But is it too little, too late? Monoclonal antibodies for COVID in full supply, but lack demand: HHS (usatoday.com). On January 17, 2021 in Infection Control Today, Kavanagh K: As Vaccine Rollout Stalls, Move Monoclonal Antibodies Into COVID Fight (infectioncontroltoday.com) using monoclonal antibodies prophylactically to protect in exposures. Both monoclonal antibodies and COVID-19 Convalescent Plasma are Passive Immunization therapeutic agents and should therefore be administered at the same appropriate time: <72 hours from symptomatology or COVID-19 positivity instead of only to patients at deaths-door. Over the last 10 months, the American public has been so misdirected (or lied to) by the ambiguity in the terminology and focus on vaccine production that few realize that Passive Immunization includes polyclonal antibodies (COVID-19 Convalescent Plasma) and monoclonal antibodies which should be given to all immediately when they become COVID-19 positive!
- 13. As is now being reported in the press, mutations of COVID-19 are developing around the World that may make the present vaccines and monoclonal antibodies ineffective.
- 14. As we go forth, the Standard-of-Care should be the following:
 - A. For those of the present 330 million Americans that are not yet infected (immunologically naïve to the disease COVID-19 negative), they should all be encouraged to receive one of the COVID-19 vaccines.
 - B. Every American who has had COVID-19 and is recovered by at least 14 days should be encouraged to donate COVID-19 Convalescent Plasma. https://www.aabb.org/for-donors-patients/give-blood
 - C. Every American who turns COVID-19 positive or becomes symptomatic (even if they have received a COVID-19 vaccine), should be afforded some form of *Passive Immunization* by the early-in-the-disease treatment with COVID-19 Convalescent Plasma/Sera or Monoclonal Antibiodies
 - D. As the COVID-19 mutations spread and the vaccines may be less effective, every American who turns COVID-19 positive or becomes symptomatic should be afforded *Passive Immunization* of COVID-19 Convalescent Plasma/Sera matching the COVID-19 mutation. Waiting for the development of a vaccine (or monoclonal antibodies) specific for the new COVID-19 mutation and withholding mutation specific COVID-19 Convalescent Plasma would be unconceivable and tantamount to patient abandonment. Every time the coronavirus mutates, it will take months to develop a new vaccine or a new monoclonal antibody—yet convalescent plasma effective against every next mutation will be available 14 days after the first human recovers from each new mutation of the coronavirus through plasmapheresis donation.
 - E. When Kidney Transplantation was considered *Investigational* in the 1960s and 1970s and the insurance industry would not pay for Kidney Transplantation as it was "Experimental", the Congress permitted for two decades the Attending Surgeons of Washington University SOM (Drs. Newton and Anderson) and Saint Louis University SOM (Drs. Maginn, Codd, and Garvin) to perform kidney transplants on both Veterans and civilians at the John Cochran (St. Louis) VAMC. Thus, the precedent six

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decades ago was set to employ the largest federal hospital system (both hospitals and CBOCs) in the nation of the Veterans Health Administration (VHA) to establish infusion centers to provide *Passive Immunization* in the treatment of COVID-19 for both Veterans and civilians.

F. Thomas Jefferson's replacement of John Locke's "property" with "the pursuit of happiness" in the *Declaration of Independence* was no mistake. We as American physicians should be leery of any potential inherent conflict-of-interest of *Industry's* and *Medicine's* working together possibly to the detriment of our patients. *De facto,* Medicine, the U.S. Government, and most of the World have publicly discredited polyclonal COVID-19 Convalescent Plasma (and Sera) while elevating monoclonal antibodies as viable early treatments in COVID-19 positivity—they are both *Passive Immunization* therapies. Every time the coronavirus mutates, it will take months to develop a new vaccine or a new monoclonal antibody—yet convalescent plasma effective against every next mutation will be available 14 days after the first human recovers from each new mutation of the coronavirus through plasmapheresis donation. The present situation throughout the World today is analogous to that of the mythological Sisyphus pushing the rock up the hill only for it upon nearing the top of the hill rolling back down for eternity.

After having viewed the abridged version of your interview on January 24, 2020 (Full interview: Dr. Deborah Birx on "Face the Nation" - YouTube) with Margaret Brennan, in my eyes you have throughout your professional life been a dedicated Military and Civil Service physician for individual patients and patients in the aggregate. Both you and I are professionally of the same generation. When we graduated, you from Penn State Univ SOM in 1980 and I in 1979 from Saint Louis Univ SOM, we both swore *Primum non Nocere* in the care of all of our patients throughout our future lives as physicians. As I viewed the interview last Sunday, I saw a physician who loves her country and has dedicated her life as a physician to bettering all patients' lives. It is your duty, my duty, and all physicians' duty by our oaths of *Primum non Nocere* to advocate for not just the <u>preventative</u> measures of *Active Immunization* but also <u>all</u> potential <u>therapeutic</u> measures of *Passive Immunization*.

It would be my hope that this correspondence will be your introduction to President Biden to explain your suggestions and thoughts on our future therapy—both *Active Immunization* and *Passive Immunization*—for all Americans. As Dr. Fauci is the President's Chief Medical Advisor on the USA COVID-19 epidemic, I will forward this letter to him, the NIH, and the FDA to help facilitate your meeting with the President. My previous Letter to the Editor of *The New England Journal of Medicine* has not been published but was probably partially the impetus for the *NEJM* publishing on January 6, 2021: Libster R, *et al*: Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (nejm.org)—I will be sure to include the Editors of the *New England Journal of Medicine* in this correspondence today. Over the past year, I have submitted three items (listed below) to the U.S. Copyright Office of the Library of Congress to preserve the chronology of what has occurred for history. With any and all of my correspondence regarding our present COVID-19 epidemic, I will dutifully provide all that is asked of me by the U.S. Federal Government as it is my duty as a physician and surgeon of the Veterans Health Administration, U.S. Department of Veterans Affairs.

- 1. Andrus CH: *Time*: The Crucial Independent Variable of the COVID-19 Pandemic. U.S. Copyright Office, June 8, 2020. TXu002199029
- 2. Andrus CH: Mayo Clinic "Safety Update" should be Classified as a Completed Phase I Trial of COVID-19 Convalescent Plasma. July 22, 2020. TXu002214049
- 3. Andrus CH: 1 Dear Mr. President PLEASE COVID-19 Convalescent Plasma NOW 11-17-2020. November 18, 2020. TXu002232947

On the evening of January 20, 2021, the America public was reminded of past Presidential inaugural addresses:

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President Abraham Lincoln's 2nd Inaugural Address includes the lines that I, as a VA physician and surgeon, and we as Americans have promised:

With malice toward none; with charity for all; with firmness in the right, as God gives us to see the right, let us strive on to finish the work we are in; to bind up the nation's wounds; to care for him who shall have borne the battle, and for his widow, and his orphan; to do all which may achieve and cherish a just, and a lasting peace, among ourselves, and with all nations.

That night, the most famous line of President Kennedy's was part of what was recited: "And so, my fellow Americas: ask not what your country can do for you—ask what you can do for you country." Dr. Birx, both you and I were in grammar school when the final lines of JFK's address were spoken that are most *apropos* to our present crisis and that for all time:

My fellow citizens of the world: ask not what America will do for you, but what together we can do for the freedom of man.

Finally, whether you are citizens of America or citizens of the world, ask of us here the same high standards of strength and sacrifice which we ask of you. With a good conscience our only sure reward, with history the final judge of our deeds, let us go forth to lead the land we love, asking His blessing and His help, but knowing that here on earth God's work must truly be our own.

Dr. Birx: Godspeed.

Respectfully,

Charles H. Andrus, M.D., F.A.C.S.
Professor, Department of Surgery, Saint Louis University School of Medicine
Chief, Unit II General Surgery (SLU GS division), St. Louis (John Cochran division) VAMC

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Beeper: 314-491-2417

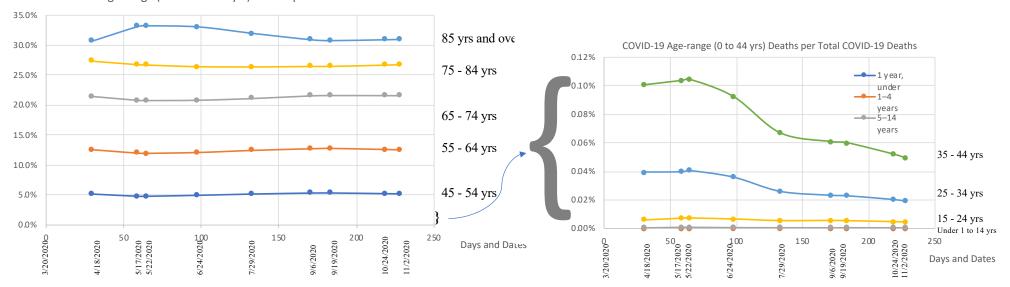
My wife's, Pamela Bergkamp Andrus's, cell phone: 314-809-9634

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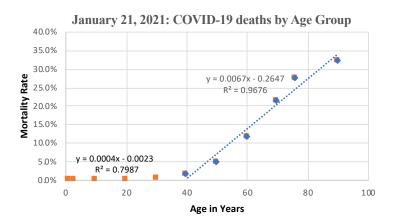
63.0 102 COVID-19 age-range deaths 2-1-2021 !!!!!!..pdf

COVID-19 Age-range (45 to over 85 yrs) Deaths per Total COVID-19 Deaths



January 21, 2021: COVID-19 Deaths by Age Group

All ages	100%
0.5 yrs	0.011%
2.5 yrs	0.006%
9.5 yrs	0.017%
19.5 yrs	0.151%
29.5 yrs	0.656%
39.5 yrs	1.726%
49.5 yrs	4.690%
59.5 yrs	11.74%
69.5 yrs	21.28%
75.5 yes	27.61%
89.5 yrs	32.11%



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01 Letter to the President

02 Index

03 Paper: Early Passive Immunization and Antiviral in the Treatment of COVID-19

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05 Graph 1—2020-2021 US COVID-19 Daily New Cases and Deaths.pptx

06 Graph 2—U.S. spikes and decreases of daily deaths.pptx

07 Table 2 Confirmed COVID-19 U.S. Cases.xlsx

08 Graph 3—U.S. spikes and decreases of daily deaths.pptx

09 Table 3 U.S. Deaths Due to COVID-19.xlsx

10 COVID-19 age-range deaths

Appendix A—abbr Time Crucial Independent Variable COVID-19 Pandemic TXu002199029

202 Time Crucial Independent Variable COVID-19 Pandemic 06 7-2020 copy.pdf

212 Table 1 Demographics (1) copy.pdf

213 Table 2 Confirmed COVID-19 Cases copy.pdf

214 Table 3 Deaths Due to COVID-19 copy.pdf

215 Graphs 1 2 3 copy.pdf

216 Graph 4 Hospital Numbers copy.pdf

Appendix B—abbr Mayo Clinic Safety Update Should be Completed Phase I Trial TXu2214049

321 Classify Mayo Safety Update as Completed Phase 1 Trial of

COVID-19 Convalescent Plasma (1) copy.pdf

322 Table I – Listing of USA Trials on NIHClinicalTrials 7-6-2020 (1) copy.pdf

323 Table II – Mayo Clinic study morbidity and odds of dying copy.pdf

Appendix C – Copy of letters sent to 537 Congressional offices August 2020

01 Dear Members of Congress and President Trump 8 23 2020

02 Dear Members of the US House of Representatives 8 28 2020

Appendix D Abbr Mr President PLEASE COVID-19 Covalescent Plasma TXu002232947

431 Dear Mr PresidentCOVID-19 Convalescent Plasma NOW 11-17-2020 (1) copy.pdf

432 Table I Excerpts from WH briefings etc 11-14-2020 copy.pdf

433 Table II Availability of Passive Immunization 11-15-2020 copy.pdf

434 FDA recommendations 11 14 2020 copy.pdf

Appendix E—Correspondence with VA and NEJM Dec 2020

505.1 Remdesivir VA corr from Nov 2020 to 12 24 2020.pdf

510 12 20 2020 response to the VHA USH.pdf

541 Letter to NEJM editor 12 13 2020 (1) copy.pdf

542 Appendix 1—Excerpts regarding Passive Immunization (1) copy.pdf

543 Appendix 2A—Remdesivir ERAs and NDA no 214787 (1) copy.pdf

544 Appendix 2B—RE Remdesivir VA communication is 12-15-2020 copy.pdf

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545 Appendix 2C—VACO Remdesivir (VEKLURY) Criteria for Use
November 2020(1) copy.pdf
546 Appendix 3—Ethical Issues (1) copy.pdf
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Appendix F—Letter to Dr. Birx 2-1-2021 *et. al.* with attachments indexed below 101 E-mail to Dr. Birx 2-1-2021 (1) copy.pdf 102 COVID-19 age-range deaths 2-1-2021 copy.pdf

Can be found in Appendix A

202 Time Crucial Independent Variable COVID-19 Pandemic 06 7-2020 copy.pdf

212 Table 1 Demographics (1) copy.pdf

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215 Graphs 1_2_3 copy.pdf

216 Graph 4 Hospital Numbers copy.pdf

Can be found in Appendix B

321 Classify Mayo Safety Update as Completed Phase 1 Trial of COVID-19 Convalescent Plasma (1) copy.pdf

322 Table I – Listing of USA Trials on NIHClinicalTrials 7-6-2020 (1) copy.pdf

323 Table II – Mayo Clinic study morbidity and odds of dying copy.pdf

Can be found in Appendix D

431 Dear Mr PresidentCOVID-19 Convalescent Plasma NOW 11-17-2020 (1) copy.pdf

432 Table I Excerpts from WH briefings etc 11-14-2020 copy.pdf

433 Table II Availability of Passive Immunization 11-15-2020 copy.pdf

434 FDA recommendations 11_14_2020 copy.pdf

Can be found in Appendix E

505.1 Remdesivir VA corr from Nov 2020 to 12 24 2020.pdf

510 12 20 2020 response to the VHA USH.pdf

541 Letter to NEJM editor 12_13_2020 (1) copy.pdf

542 Appendix 1—Excerpts regarding Passive Immunization (1) copy.pdf

543 Appendix 2A—Remdesivir ERAs and NDA no 214787 (1) copy.pdf

544 Appendix 2B—RE Remdesivir VA communicationjs 12-15-2020 copy.pdf

545 Appendix 2C—VACO Remdesivir (VEKLURY) Criteria for Use

November 2020(1) copy.pdf

546 Appendix 3—Ethical Issues (1) copy.pdf

Appendix G—NIH and FDA responses including establish NIAID Case #12276 6-10-2020 NIH and FDA responses including 6-6-2020 re NIAID Case #12276.pdf

Timeline Bibliography 2021-06-04 Master References

Submission 09-12-2023 of BOOK1 Dear Mr. President -- COVID-19 and Where we went WRONG



65.0 NIH and FDA responses including 6-10-2020 re NIAID Case #12276.pdf DEPARTMENT OF HEALTH & HUMAN SERVICES Public Harden \$1266

National Institutes of Health National Institute of Allergy and Infectious Diseases Bethesda, Maryland 20892

June 10, 2020

Dr. Charles Andrus 150 Emerald Green Court St. Louis, MO 63141

NIAID Case #12276

Dear Dr. Andrus:

Thank you for your recent fax directed to Anthony S. Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health. Due to his professional responsibilities, Dr. Fauci has asked me to respond on his behalf.

Thank you for sharing this information.

Sincerely,

Kara M. Harris, MPH
Section Chief for Controlled Correspondence and Public Inquiries
Legislative Affairs and Correspondence Management Branch
Office of Communications and Government Relations
National Institute of Allergy and Infectious Diseases
National Institutes of Health

DISCLAIMER: NIAID does not endorse or recommend any commercial products, processes, or services. The views and opinions of authors expressed on the NIAID website do not necessarily state or reflect those of the U.S. government and may not be used for advertising or product endorsement purposes. Any non-government resources are provided for your convenience. NIAID is not responsible for the availability, content, or privacy policies of non-federal organizations' materials or websites, nor does NIAID endorse, warrant, or guarantee the products, services, or information described or offered by such organizations. Non-federal public websites do not necessarily operate under the same laws, regulations, and policies as federal websites. It is not the intention of NIAID to provide specific medical advice, but rather to provide users with information to better understand their health and their diagnosed disorders. Specific medical advice will not be provided, and NIAID urges you to consult with a qualified physician for diagnosis and for answers to your personal questions.

150 Emerald Green Court St. Louis, MO. 63141 314-455-9482

June 7, 2020

Anthony S. Fauci, M.D.
Director of the U.S. NIAID
U.S. National Institutes of Health
U.S. Dept of Health & Human Services
5601 Fishers Lane, MSC. 9806
Bethesda, MD. 20892-9806

Phone: 310-496-5717 FAX: 301-402-3573 Stephen Hahn, M.D.
Commissioner, U.S. Food and
Drug Administration
U.S. Dept of Health & Human Services
c/o CBER Ombudsman
Center for Biologics Evaluation and
Research (CBER)
10903 New Hampshire Ave, W071-7240
Silver Springs, MD. 20993-0002
Phone: 301-796-8240

Re: Submission of: Time: The Crucial Independent Variable of the COVID-19 Pandemic

Dear Drs. Fauci and Hahn:

On April 5, 2020, I submitted to the President and yourselves, the attached correspondence advocating for establishment of a national program through the Blood Banks of America for:

...systematic collection and safety testing of convalescent plasma from COVID-19 survivors. Such a national coordinated project could provide possible subsequent initial passive immunization with convalescent plasma to those infected with the corona virus until each individual can develop his/her own serum antibodies over the immediate subsequent symptomatic 14-day period.

The U.S. Food and Drug Administration is now providing rapid response for eIND applications regarding convalescent plasma and also is participating in the collaboration with the Mayo Clinic for physician and site recruitment. I have attached a regression analysis comparing the aggregate results of the efforts of the last several months in containment and resolution of the COVID-19 epidemics in the countries of China, Italy, Spain, and the United States of America. At present, public and local physician knowledge of the FDA IND research protocols (including that of the Mayo Clinic convalescent plasma project) are not well-known. Thus, the motivation for the attached paper entitled:

Time: The Crucial Independent Variable of the COVID-19 Pandemic

I will provide a CD containing the paper and Excel databases with the raw data and calculations so that the methodology can be critically evaluated. I will submit this cover letter and other cover letters with the manuscript (including tables and graphs) and attachments to the U.S. Copyright Office for recording for history this submission. As this is a submission to history and

not in regards for any personal gain, I waive all copyright protections regarding the reproduction of this paper. I hope this information will be helpful to you.

I will also submit this compilation to Catherine DeAngelis, M.D. and Jeffrey Drazen, M.D., former editors-in-chief of the Journal of the American Medical Association and The New England Journal of Medicine as their involvement—although they probably don't realize it-was helpful in my previous advocacy^{1.9} to discontinue operations performed by surgery residents in the VA with the affiliated-University Attending Surgeon-of-Record in absentia. (Congress has never allowed for the Veterans Health Administration subvention—ability for the VA to bill Medicare—and thus Intermediary Letter-372 (Supervision Rules regarding Teaching Physicians of the U.S Department of Health and Human Services) does not directly apply to the Veterans Health Administration, U.S. Department of Veterans Affairs. Today, VHA Handbook 1400.01 no longer permits any elective or urgent operations to be performed by surgery residents without the Attending Surgeon-of-Record being physically present during at least the critical portions of every operation. Thank you for considering this submission.

Respectfully,
(Lanco H Hadeus M)

Charles H. Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine

Chief of the Unit II (SLU) General Surgery division,

Surgical Service, John Cochran (St. Louis) VAMC

References 1-9: See attached titles from the U.S. Copyright office

Attachments:

- 1. Paper entitled: Time: The Crucial Independent Variable of the COVID-19 Pandemic
- 2. CD containing an electronic copy of the paper, the Excel databases
- 3. Copies of cover letters to other recipients
- 4. Copy of the submission of April 5, 2020



July 29, 2020

Dr. Charles H. Andrus 150 Emerald Green Court St. Louis, MO 63141

Dear Dr. Andrus:

Thank you for your letter seeking information from the Food and Drug Administration (FDA) and the National Institutes of Health regarding the clinical development, safe use and availability of convalescent plasma collected from individuals who have recovered from Coronavirus Disease 2019 (COVID-19).

We appreciate your interest in this important topic and hope that the following information will be helpful.

Because COVID-19 convalescent plasma has not yet been approved for use by FDA, it is regulated as an investigational product. Health care providers or acute care facilities should instead obtain COVID-19 convalescent plasma from an FDA-registered blood establishment and must participate in one of the pathways described below.

1. Clinical Trials

Investigators wishing to study the use of convalescent plasma in a clinical trial should submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR Part 312). CBER's Office of Blood Research and Review is committed to engaging with sponsors and reviewing such requests expeditiously. During the COVID-19 pandemic, INDs may be submitted via email to CBERDCC eMailSub@fda.hhs.gov.

2. Expanded Access

An IND application for expanded access is an alternative for use of COVID-19 convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 CFR 312.305). FDA has worked with multiple federal partners and academia to open an expanded access protocol to facilitate access to COVID-19 convalescent plasma across the nation. Access to this investigational product may be available through participation of acute care facilities in an investigational expanded access protocol under an IND that is already in place.

Currently, the following protocol is in place: National Expanded Access Treatment Protocol.

Further information, including a protocol summary, are available at:

https://www.uscovidplasma.org/

https://www.uscovidplasma.org/pdf/COVID-19%20Plasma%20EAP.pdf

3. Single Patient Emergency IND

Although participation in clinical trials or an expanded access program are ways for patients to obtain access to convalescent plasma, for various reasons these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the COVID-19 pandemic presents, and while clinical trials are being conducted and a national expanded access protocol is available, FDA also is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of the patient's physician requesting a single patient emergency IND (eIND) for the individual patient under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization, if the applicable regulatory criteria are met.

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Note, in such case, a licensed physician seeking to administer COVID-19 convalescent plasma to an individual patient must request the eIND (see 21 CFR 312.310(b)).

Information about patient and donor eligibility can be found at:

https://www.fda.gov/vaccines-blood-biologics/investigational-new-rirug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

Additional background about COVID-19 is available on the FDA website at:

https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19

We hope this information is helpful. If you have questions, please feel free to contact us at <u>ocod@fda.hhs.gov</u> or by phone at 1-800-835-4709.

Sincerely,

Laura B. Carter -S

Laura Carter

Health Communications Specialist Center for Biologics Evaluation and Research Office of Communications, Outreach and Development U.S. Food and Drug Administration

Tel: 800-835-4709 OCOD@fda.hhs.gov





This informal communication represents my best judgment at this time. It does not constitute an advisory opinion in accordance with 21 CFR 10.85, and does not necessarily represent the formal position of FDA or otherwise obligate the agency to the views expressed.

U.S. Food & Drug Administration 10903 New Hampshire Avenue Silver Spring, MD 20993

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SILVER SPRING .MD 20903

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CONSUMER AFFAIRS BRANCH U.S. FOOD & DRUG ADMINISTRATIO 10903 NEW HAAPSHIRE AVE SILVER SPRING MD 209930002	,
SHIP TO: DR. CHARLES H. ANDRUS 150 EMERALD GREEN COURT SAINT LOUIS MO 63141-7541	
MO 630 9-41	
UPS NEXT DAY AIR SAVER 1 P	
	ſ
strong st	
CENTER: CBER Center/Office: cber/om	*************



September 14, 2020

Charles Andrus, M.D., F.A.C.S.
Saint Louis University
Health Sciences Center, School of Medicine
Department of Surgery
150 Emerald Green Ct.
St. Louis, MO 63141

Dear Dr. Andrus,

Thank you for your inquiry regarding COVID-19 convalescent plasma. The FDA appreciates your concerns about ensuring access to COVID-19 convalescent plasma during the public health emergency. Your inquiry was forwarded to the FDA's Center for Biologics Evaluation and Research for response.

As noted in your letter, since April 2020, the FDA has facilitated access to investigational COVID-19 convalescent plasma through several investigational pathways. A national expanded access program was initiated in early April to fill an urgent need to provide patient access to a medical product of possible benefit during a time that the FDA was working with researchers to facilitate the initiation of randomized clinical trials to study convalescent plasma. The program was developed with funding from the HHS' Biomedical Advanced Research and Development Authority (BARDA), with the Mayo Clinic serving as the lead institution. The program has facilitated the transfusion of over 70,000 patients with convalescent plasma. The FDA has also facilitated access to convalescent plasma for treating COVID-19 through traditional clinical trials and emergency single-patient investigational new drug (IND) applications.

On August 23, 2020, in response to the public health emergency and the FDA's extensive review of the science and data generated over the past several months, the agency issued an emergency use authorization (EUA) for investigational COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The Letter of Authorization and associated materials are available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

In deciding to move forward with the EUA, the FDA determined that it was reasonable to believe that COVID-19 convalescent plasma may be effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients. The agency also determined that the known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product and that there are no adequate, approved, and available alternative treatments.

U.S. Food & Drug Administration 10903 New Hampshire Avenue Silver Spring, MD 20993 www.fda.gov



The EUA is not intended to replace randomized clinical trials and facilitating the enrollment of patients into any of the ongoing clinical trials is critically important for the definitive demonstration of safety and efficacy of COVID-19 convalescent plasma. The FDA continues to recommend that the designs of ongoing randomized clinical trials of COVID-19 convalescent plasma and other therapeutic agents remain unaltered, as COVID-19 convalescent plasma does not yet represent a new standard of care based on the current available evidence.

Given the paucity of alternative treatments, the EUA is intended to improve the availability of COVID-19 convalescent plasma, while the FDA continues to work with researchers to conduct the clinical trials necessary for the definitive demonstration of COVID-19 convalescent plasma efficacy.

Additionally, on September 2, 2020, the FDA revised guidance entitled, "Investigational COVID-19 Convalescent Plasma" to provide recommendations to health care providers and investigators on the use of COVID-19 convalescent plasma under the EUA or investigational convalescent plasma under an IND during the public health emergency. The guidance supersedes the guidance of the same name dated April 2020, and updated in May 2020, and provides additional information related to the recently issued EUA for the use of COVID-19 convalescent plasma to treat hospitalized patients with COVID-19, including a discussion to facilitate the availability of this product when blood establishments, hospitals, and health care providers collect plasma that does not meet the Conditions of Authorization of the EUA.

The guidance also describes FDA's interim compliance and enforcement policy regarding the IND requirements for the use of investigational convalescent plasma. The guidance explains that during this period of enforcement discretion and beyond, the FDA will continue to work with any investigators who wish to submit INDs for the study of investigational convalescent plasma. Health care providers are encouraged to enroll patients and complete clinical trials.

In closing, we want to take this opportunity to thank you and your colleagues for treating COVID-19 patients and your interest in advocating on your patients' behalf.

Sincerely,

Jill S. Burkoff -S Discussion Use Search of the State of the Search of t

Center for Biologics Evaluation and Research
Office of Communication, Outreach and Development
U.S. Food and Drug Administration
Tel: 240-402-8021
OCOD@fda.hhs.gov

U.S. Food & Drug Administration 10903 New Hampshire Avenue Silver Spring, MD 20993 www.fda.gov

Submission 09-12-2023 of BOOK1 Dear Mr. President -- COVID-19 and Where we went WRONG

6/5/2021 RE: Thank you Dr. Birx for your discussion on Face the Nation of 1/24/2021

From: afauci@niaid.nih.gov,

To: candrus600@aol.com,

Subject: RE: Thank you Dr. Birx for your discussion on Face the Nation of 1/24/2021

Date: Mon, Feb 15, 2021 10:57 am

My work with the Coronavirus Task Force and the large volume of incoming emails precludes me or my staff from answering each individual message. I would encourage you to visit www.coronavirus.gov for the latest information and guidance related to COVID-19.

Thank you, and best regards.

Anthony S. Fauci, M.D.

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66.0 01 Andrus SLU cv 8_11_2021.pdf

Revised August 10, 2021

CURRICULUM VITAE

Charles H. Andrus, M.D., F.A.C.S.

A. Personal Information:

Home address 150 Emerald Green Court

Creve Coeur, MO 63141

(314) 455-9482

Marital status Married

Birth Date March 28, 1953

Citizenship U.S.

B. Education:

Undergraduate degree and major

University of San Francisco, 1971-1975 San Francisco, CA 94117 BS in Chemistry (Amer. Chemical Soc. approved degree) summa cum laude

Cal State University at San Francisco, 1972-73 (summers) 1600 Holloway Ave.
San Francisco, CA 94132
General Zoology and General Botany

Graduate degree and major

Saint Louis University School of Medicine, 1975-79 1402 South Grand Blvd. St. Louis, MO 63104 M.D. conferred May 12, 1979

Postgraduate training

Saint Louis University - Pediatrics, 1979-81 Cardinal Glennon Memorial Hospital for Children 1465 South Grand Blvd. St. Louis, MO 63104

Saint Louis University - General Surgery, 1981-86 3635 Vista Avenue at Grand Blvd. P.O. Box 15250 St. Louis, MO 63110-0250 ABS Board Certification - Feb. 25, 1987

Surgical Endoscopy, 1987 Mt. Sinai Medical Center One Mt. Sinai Drive Cleveland, OH 44106-4198

C. Board certification and Licensure:

Passed National Boards:

1977 Part I (6/77) 1978 Part II (9/78) 1980 Part III (3/80)

certified 07/01/80 No. 216934

American Board of Surgery

7/13/06

10/28/06

Identification #042223 Certification No. 32104 2/25/1987

Recertified 1994 until July 1, 2007
Recertified 2006 until July 1, 2017
Recertified 2014 until December 31, 2027

MOC (Maintenance of Certification) update 12/2012 and then recertification 2014

NPI 1689611840 UPIN No. 12496

Expiration Date

10/28/2018

9/19/1980	Missouri State R8A85	1/31/2022
1996	Illinois 036-093146	7/31/2023
11/7/2001	California G86301	3/31/2023
1980	DEA number	6/30/2022
2/29/2005	Missouri BNDD	2/28/2022
4/9/2004	ATLS ID 84101 Instructor	10/28/2018
10/2005	BLS—Healthcare Provider	08/31/2022
April 2009	ACLS Provider	09/30/2022
June 2006	PALS Provider PALS Instructor ID#04120093288	06/2018

ATLS CS#28326

ATLS Instructor 84101

AMA# 02834790044 ACS fellow since 1990

ge 1163 of 1

California mandated CME in pain management and the treatment of terminally ill and dying patients per California Assembly Bill No. 487:

4/27/2002 6 units "Meeting the Challenge—A conference on Pain Management and

End of Life Care"

Sponsored by the Department of Family Practice, San Joaquin General

Hospital and the Hospice of San Joaquin. Stockton, CA.

10/4/2003 4 units "Living While Dying: End of Life Care." Sponsored by Kaiser

Permanente Northern California Region, Stockton, CA.

12/4/2004 2 units Pain Management & Alzheimer's Disease /

Dementia Symposium

Sponsored by Sutter Medical Center, Sacramento, CA. (Please note, the pain management approved CME was 2 hours and 5 minutes of the total

3.75 CME credit hours. I attended the entire 3.75 hours)

Total 12 units

D. Current position and address:

Professor. Department of Surgery (Tenured July 1, 2009), Saint Louis University School of Medicine

Saint Louis University faculty of the Surgical Service, John Cochran VAMC (St. Louis VAMC) August 7, 2016 to present

Member of the SLU Surgery Resident Review Clinical Competency Committee from VA, July 2017- to present

Faculty Advisor for Surgery Resident Research Nov, 2012 to present

General Surgery Residency Program Director July 1, 2009 - Nov, 2012

General Surgery Residency VA Site Director 11/2019 - present

General Surgery, Trauma Surgery, and Surgical Endoscopy 3635 Vista at Grand Blvd. P.O. Box 15250 St. Louis, MO 63110-0250

Trauma Office (314) 577-8563, (314) 577-8802

Direct Office (314) 577-8567

e-mail:charles.andrus@health.slu.edu (old SLU e-mail:

andrusmd@slu.edu)

Fax: (314) 268-5194

SLUCare Doctors Office Building 3660 Vista Avenue, Room 108 St. Louis, MO 63110 (314) 977-6125

08/07/2016- Active Medical Staff

to present Staff General Surgeon, Unit II Surgery

St. Louis (John Cochran) VAMC

Surgical Service (112) 915 N Grand Blvd St. Louis, MO 63106

Surgery Office: 314-289-6363, 314-652-4100 ext 54463

Office phone: 314-652-4100, ext 54463

09/2006-Present Active Medical Staff

SSM Cardinal Glennon Children's Medical Center

1465 South Grand Blvd. St. Louis, MO 63104

4/2005-present Active Medical Staff

SSM DePaul Health Center

12303 DePaul Drive

Bridgeton, MO 63044-2588

9/2006 to pres St. Mary's Health Center -- (Active Staff)

6420 Clayton Rd. St. Louis, MO 63117

E. Previous Professional Experience:

1986-1988 Clinical Instructor in General Surgery

Saint Louis University School of Medicine

St. Louis, MO

1988-1992 Assistant Professor in General Surgery

Saint Louis University School of Medicine

St. Louis, MO

1992-1996 Associate Professor in General Surgery

Saint Louis University School of Medicine

St. Louis, MO

1992-1996 Associate Professor of General Surgery

and Director of Surgical Endoscopy Saint Louis University School of Medicine

St. Louis, MO

Saint Louis University Medical Center

General Surgery Department 3635 Vista Ave. at Grand Blvd.

P.O. Box 15250

St. Louis, MO 63110-0250

(314) 577-8372

Department of Surgery (112/JC) St. Louis Veteran's Administration Medical Center 915 North Grand Blvd. St. Louis, MO 63106 (314) 652-4100, ext. 4328 / (314) 289-6363

8/1996-12/2001 Vice Chairman, Department of Surgery

Professor of General Surgery and Director of Surgical Endoscopy Loyola University School of Medicine 2160 South First Avenue Maywood, IL 60153 (708) 327-2899

Chief of Surgery (112) Edward Hines Jr., Veteran's Administration Hospital P.O. Box 5000 Hines, IL 60141-5000 (708) 202-2036

2/2002-4/2005 Vice Chairman, Department of Surgery

Chief, Surgical Endoscopy Chairman, SJGH Tissue and Transfusion Committee San Joaquin General Hospital P.O. Box 1020 Stockton, CA 95201

(209) 468-6620; fax (209) 468-6248

email: candrus@sjgh.hs.co.san-joaquin.ca.us

4/2005-9/2006 Medical Director, Trauma Services

SSM DePaul Health Center 12303 DePaul Drive

Bridgeton, MO 63044-2588

EMS Office (314) 344-7463

email: Charles_Andrus@SSMHC.com

fax (314) 344-7590

Physician Office Building: 12255 DePaul Drive, Suite 445 St. Louis, MO 63044-2588 (314) 344-7299

9/2006-11/14/07 Professor of Surgery

Medical Director, Trauma Services

Department of Surgery

Saint Louis University School of Medicine

3635 Vista at Grand Boulevard

P.O. Box 15250

St. Louis, MO 63110-0250

09/2006-Present **Active Medical Staff**

11/14/07-8/1/08 Interim Director of Surgery.

SSM Cardinal Glennon Children's Med Center

10/2007-8/1/2008 Co-Director, Pediatric Trauma

SSM Cardinal Glennon Children's Medical Center

1465 South Grand Blvd. St. Louis, MO 63104

Pediatric Surgery Office: (314) 577-5629; Fax (314) 268-6454; Clinic (314) 268-4010

09/2006-Present Professor of Surgery (Tenured 7/1/2009)

7/2009-11/2012 General Surgery Residency Director, Department of Surgery,

Saint Louis University School of Medicine

Department of Surgery Advisor of Resident Research 11/2012-present

Department of Surgery

Saint Louis University School of Medicine

3635 Vista at Grand Boulevard

P.O. Box 15250

St. Louis, MO 63110-0250

F. Clinical Staff appointments:

7/1986-7/1996 Department of Surgery

> Saint Louis University Hospital 3635 Vista Avenue at Grand Blvd.

P.O. Box 15250

St. Louis, MO 63110-0250

7/1986-7/1996 General Surgery Staff - Unit II Surgery

John Cochran VAH 915 North Grand Blvd. St. Louis, MO 63106 (314)-652-4100 ext. 4328

St. Mary's Health Center -- (Courtesy Privileges) 4/1988-7/1996

> 6420 Clayton Rd. St. Louis, MO 63117

9/2006 to pres St. Mary's Health Center -- (Active Staff)

6420 Clayton Rd. St. Louis, MO 63117

9/1990-8/1996 9/2006-pres Cardinal Glennon Children's Hospital

1465 South Grand Blvd. St. Louis, MO 63104

(Active Staff)

8/1996-12/2001 Foster G

Foster G. McGaw Hospital Department of Surgery Loyola University, Chicago Stritch School of Medicine 2160 South First Avenue Maywood, IL 60153 (708) 327-2899

8/1996-1/2002

Edward Hines, Jr. VAH Surgical Service (112)

P.O. Box 5000

5th Avenue & Roosevelt Street

Hines, IL 60141-5000 (708) 202-2036

2/2002-6/2006

San Joaquin General Hospital Department of Surgery 500 West Hospital Road French Camp, CA 95231

(209) 468-6620

4/2005-present

SSM DePaul Health Center Bridgeton, MO 63044-2588

(314) 344-7463

9/2006-pres

Saint Louis University 3635 Vista at Grand Blvd.

P.O. Box 15250

St. Louis, MO 63110-0250

(314) 577-8567

9/2006-pres

SSM Cardinal Glennon Children's Medical Center

1465 South Grand Boulevard

St. Louis, MO 63104 (314) 577-5618

8/2007 - 5/2009 5/2009 - 12/2013 8/7/2016-present General Surgery Staff - Unit II Surgery (Consultant) General Surgery Staff - Unit II Surgery (Active Staff) General Surgery Staff - Unit II Surgery (Active Staff)

John Cochran VAH 915 North Grand Blvd. St. Louis, MO 63106

Page 1168 of 1266 8

Charles H. Andrus, M.D., F.A.C.S.

(314)-652-4100, ext. 54463

G. Professional Society Membership:

1975-1988	American Chemical Society
1975-pres	American Medical Association
1982-1996	Missouri State Medical Association
1982-1996	St. Louis Metropolitan Medical Society
1987-2002	Society of American Gastrointestinal Endoscopic Surgeons (SAGES)
1987-1990	American College of Surgeons (Candidate Group)
1988-pres	Association for Surgical Education
2009-pres	Association of Program Directors in Surgery
1988-1997 2005-to present	St. Louis Surgical Society 1992-1995 Counselor 1996 President-elect, (Moved to Chicago in the Summer of 1996, but organized and presented the Fall Panel in November 1996.) Member, St. Louis Surgical Society
·	
1988-2002	American Society of Gastrointestinal Endoscopy
1988-2002	The Association of Veteran's Administration Surgeons
1989-1993	Southern Medical Association
1989-2002	The Southwestern Surgical Society
1990-pres 2007-pres	American College of Surgeons (Fellow) Annual <i>ad hoc</i> fellowship interviewer
1990-1996 2012 to present	Fellow - American College of Surgeons - Missouri Chapter
2012-2015	State Councilor to the Board, MO Chapter, American College of Surgeons
2015-2017	Vice-President, Missouri Chapter, American College of Surgeons
5/2017 - 5/2018	President, Missouri Chapter, American College of Surgeons
5/2018-to present	Past President, Missouri Chapter, American College of Surgeons
1991-1998	The Society of Laparoendoscopic Surgeons

1993-2002	American Gastroenterological Association
1993-2002	Association for Academic Surgery
1996-2002	Society of Surgeons of the Alimentary Tract
1997-2002	Chicago Surgical Society
1999-2002	American College of Physician Executives

NB: Due to indebtedness incurred during my advocacy for Veteran Patients in the litigation of *Andrus v VA* (US Court of Appeals for the Federal Circuit, Case 03-3162), only the American Medical Association, the American College of Surgeons, the St. Louis Surgical Society, the Association for Surgical Education, and the Association of Program Directors in Surgery dues were continued.

H. Honorary Societies, Honors and Awards:

1974-pres	Alpha Sigma Nu-Nat'l Jesuit Honor Society
1980	Candlelighter's Award - Outstanding resident involved in the care of hematologic-oncology patients
1984	House Officer of the year Saint Louis University
1991	AMA Physician's Recognition Award in Continuing Medical Education
1994	Listing in American Men and Women of Science
1994-1995	Selected Honored Member National Directory of Who's Who
1995-1996	Selected Honored Member National Directory of Excellence of Who's Who
1996	President-elect, St. Louis Surgical Society (moved to Chicago so the president term was completed by Terence Wade, M.D., F.A.C.S.)
1996-1999	AMA Physician's Recognition Award in Continuing Medical Education with Special Commendation for Self-Directed Learning
6/19/98	Attending Physician of the Year Award, Loyola University Stritch School of Medicine, "In recognition of his outstanding efforts as teacher, mentor and role model." Selected by the first year residents of the Department of Surgery at Loyola University Medical Center
2/6/99	Certificate of RecognitionPhilippine Medical Association in Chicago for being a lecturer on "Laparoscopic Surgery: A review and update."
9/27/99	DVA Special Contribution Award, Hines Hospital Nutrition Support Team/Home Infusion Program
12/10/99	Interviewed by the U.S. Department of Veterans Affairs, Veterans Health Administration 1999 Under Secretary for Health Commission for the position of Under Secretary for Health, Veterans Health Administration.

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Hines VAH Director's presentation of "A Certificate of Recognition of Excellence from the NSQIP" (VA National Surgery Quality Improvement Program) which states: "For LOW outlier status which indicates that riskadjusted outcomes were better than average VAMC in: All Non-Cardiac Surgery during fiscal year 2000."

10/19/01

At the Loyola University/Stritch School of Medicine St. Luke's Dinner Dance announced as one of the nominees for the "Faculty of the Year Award" for the last 4 consecutive years of my five years on the faculty.

12/20/01

U.S. *Department of Veterans Affairs Commendation*: "The Hospital Ethics Committee (HEC) awards this Commendation to Charles H. Andrus, M.D., Chief, Surgical Service, Edward Hines, Jr. VA Hospital and Professor of Surgery, Loyola University Stritch School of Medicine in recognition of his extraordinary courage, dedication and contributions to ethical practices in healthcare. In clinical practice and as the Chief of Surgical Service, Dr. Andrus has been an exemplary ethical practitioner and leader. As a clinician, he has been a forthright advocate of the need of compassionate, respectful and candid dialogue between patients, their family members and caregivers regarding the moral tensions and emotional turmoil that often arise at the end-of-life. His sensitivity to and advocacy for these issues and the delicate mediation and decision-making they require have been inspirational. Furthermore, in every respect, he has been an outspoken, articulate and passionate champion of the need for constant vigilance about the ethical implications of physician practices. In a most effective way, his leadership style has been his example. The entire hospital community is indebted to him for the impact that he has had on our patients and their family member. He is looked upon with great respect and held in great esteem by his colleagues who have been honored by his presence. As a result of his admirable qualities, it is with great pleasure that the HEC commends Dr. Andrus for his inspirational contributions and leadership. We wish him well and God's speed in his new endeavors.

Barbara Temeck, M.D. Gerald J. Mozdzierz, Ph.D. Chief of Staff Chairman, Hospital Ethics Committee

7/17/02

San Joaquin General Hospital—Physician Recognition Award presented by

Dale Bishop, M.D., Medical Director

12/7/07

Spirit of Saint Ignatius Service Award in recognition of extraordinary service, Department of Surgery,

Saint Louis University School of Medicine

7/8/08

"Positively Outstanding Physician", Target 100 Physician Award, Target 100

Physician Satisfaction Team, Saint Louis University Hospital

10/17/2008

St. Luke's Award: Faithful Healer. SSMCardinal Glennon Children's Medical

Center

2/4/09

5/14/2009

"Positively Outstanding Physician", Target 100 Physician Award, Target 100 Physician Satisfaction Team, Saint Louis University Hospital

The Leonard Tow Humanism in Medicine Award, The Arnold P. Gold

Foundation, awarded at the Graduation Convocation of the Class of 2009. St. Louis University School of Medicine

12 5/20/2009 2008 Saint Louis University, Department of Surgery: Best Attending Award 2008-2009 "Exceptional Pin", Cardinal Glennon's World Championship Service (WCS) program, awarded by the World Championship Service Celebration and Recognition Committee, SSM Cardinal Glennon Children's Medical Center (~6 times during this period) 2009 Top Docs, SSM Cardinal Glennon Children's Hospital, St.Louis, MO 2010-2011 Vallee L William Award for Excellence in Surgical Education, Department of Surgery, Saint Louis University School of Medicine 2011 Service Award: on behalf of the patients, families and staff of SSM Cardinal Glennon Children's Medical Center: "Many thanks for your support, skill, and compassion" 2011 Nominated for Caring Physician Award, Saint Louis University Hospital, St. Louis, MO 2013 Letter of Commendation regarding care of a patient from Philip Alderson, M.D., Dean, Saint Louis University School of Medicine, February 20, 2013 2015 Award for best teacher by last junior class evaluation, June 10, 2015

2016 "Twenty years of Dedicated Service", Saint Louis University

2018 A gavel as the outgoing President, Missouri Chapter, American College of

Surgeons

2019 Nominated (1 of 3 faculty nominees but not final awardee) for the Annual

> Overall Humanism Award: "The Humanism in Education Award" by the School of Medicine Class of 2019, Saint Louis University School of Medicine,

St. Louis, MO. (Awards Banquet, February 1, 2019)

12/2/2019 2019 VA St. Louis Medical Staff Award:

> Dr. Andrus is a staff physician in the Surgical Service's Section of General Surgery is recognized by his peers for his excellence in patient care, teaching, integrity, and research. He has over 20 years of service in VAH, and the majority of that time has been dedicated to the care of our Veterans at the John Cochran VA. Dr. Andrus is an experienced researcher and clinician and has served on numerous committees and in many leadership roles. His peers praise him for "instilling passion for surgery in his residents" and "teaching residents how to care for patients at the bedside". He has played an integral role in the day to day function and coverage of general surgery clinical services and is known for his multidisciplinary approach to patient care and commitment to considering the biopsychosocial needs of his patients. He has continued to deliver the highest quality of care to our Veterans and his colleagues and patients alike have benefited greatly from his knowledge, experience, compassion, and dedication.

6/2020 - present Annual Charles H. Andrus, M.D., F.A.C.S. for the most outstanding Surgery Intern:

2019 - 2020Kristen Dougherty 2020 - 2021**Emily Mann**

I. Professional Services:

I. Committee memberships:

10/94-1996

Saint Louis	University	Medical	Center	1986-1996
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1987-1988	Utilization Review Committee
1988-1992	Environmental Protection Committee
1987-1996	Endoscopy Committee Chairman, July 1990-June 1992
1988-1996	Chairman, Surgical Department Conference (Grand Rounds) Committee
1990-1992	Quality Improvement Committee
12/93-12/95	Board of Directors - University Medical Group (UMG)
John Cochran	Veterans Administration Medical Center 1986-1996
1987 - 1961	Chief, Unit II Surgery, Surgical Service, St. Louis VAMC
1987-1990	Quality Assurance Committee
1987-1989	Surgical Representative, Nutritional Support Committee
1988	Medical Staff Bylaws Revision Committee
1987-5/90	Medipro Surgical Reviewer for District #21
1988-1990	Medipro District Representative for District #21
1988-1989	Ad Hoc Committee for Revisions of Chief of Staff S.O.P.'s with Regards to Medications
1989-1992	Chairman, Laser Safety Committee
1990-1996	Chairman, Case Review and Tissue Committee
1990-1992	IRM Committee (Clinical Implementation of the Decentralized
	Hospital Computer Program)
11/90-8/92 10/92-11/95	Clinical Executive Board QA/QI Committee of the Medical Staff
10/94-11/95	Chairman, QA/QI Committee of the Medical Staff
10/94-1996	Secretary of the Medical Staff

Member of Professional Standards Board

14

10/94-1996	Member of the Executive Committee of the Medical Staff (ECMS)
	ex-officio

John Cochran Veterans Administration Medical Center 2016 - to present

2017 - pres	Appointed Surgical Service representative to several Root Cause analysis committees
2017 - pres	Appointed <i>ad hoc</i> reviewer for Cases submitted to the VISN and John Cochran VAMC from the Board of Veterans Appeals (BVA)
2018 - pres	Chief, Unit II General Surgery, John Cochran (STL) VAMC
2018 - pres	Saint Louis University, Department of Surgery, General Surgery residency administrator regarding Surgery residents assigned to Unit II General Surgery, John Cochran (STL) VAMC
2019 - pres	St. Louis VAMC Transfusion Committee

Edward Hines, Jr. VAH 1996 - 2002

1996 - 2002	Chief of Surgery
1996-1/01	Quality Improvement Team (discontinued)
1996-2002	Medical Executive Committee
1996-2002	Professional Standards Board
1996-1/01	Hines Stacking Committee (discontinued)
1996-2001	Dean's Committee
10/1996	Chairman, Surgical Consolidation Task Force Meeting
	(NCVAMC/Hines)
11/1996	Member, VISN 12 Cardiac Surgery Work Group
1997-2002	Member, Resources Management Committee
Spring 1998	Member, VISN 12 Cardiac Surgery Task Group
Spring 1998	Member, COS Search Committee
Spring 1998	Member, ACOS Search Committee
9/97-2002	Member and QA/Utilization Review data collector
	OR/PAR Committee

12/98-pres	Member of the Utilization Management Committee
12/98-pres	Member of the Medical Records Committee
4/00-pres	Member of the Executive Council of the Clinical Staff (ECCS)
9/00-5/01	Member of the Leadership Council
10/00-3/01	Capital Asset Realignment for Enhanced Services (CARE) Clinical
	Task Force
12/00-1/01	Member, Associate Director Search Committee
	Member of the Dean's Committee for the St. Louis VAMC

Loyola University Medical Center. 1996 - 2002

1996 - 2001	Professor and Vice-Chairman, Department of Surgery, Loyola University School of Medicine
1996-2001	Executive/Finance Committee, Department of Surgery
1997-2001	Member, Search Committee for the Chair of the Department of
	Neurosurgery
2/2001	LCME Graduate Medical Education committee member

San Joaquin General Hospital 2002 - 2005

2002 - 2005	Vice-Chairman, Department of Surgery
2002-4/2005	Chairman, Tissue and Transfusion Committee
2002-4/2005	Member, San Joaquin General Hospital Institutional Review Board
7/2003-4/2005	Vice-president/ President-elect of the Medical Staff, San Joaquin
	General Hospital Medical Staff
7/2003-4/2005	Member of the SJGH Medical Executive Committee
7/2003-4/2005	Member of the Joint Conference Committee between representatives
	of SJGH and the San Joaquin Board of Supervisors
7/2003-4/2005	SJGH Medical Staff Bylaws Committee

SSM DePaul Health Center 2005 - 2006

2005 - 2006	Trauma Medical Director
2005-2006	Chairman, Trauma Peer Review Committee
2005-2006	Member, General Surgery Peer Review Committee
2005-2006	Member, Critical Care Committee
2005-2006	Co-director, Emergency Medical Services, SSM DePaul Health Center
2005-2006	Member, Missouri District #1 Committee on Applicants of the
	American College of Surgeons
2005-2006	Member, Safety/Environmental of Care Committee

Saint Louis University Hospital

9/2005-2011	Frequent attendee, Missouri State Advisory Council to the Governor on EMS and Trauma	
2005-pres	Regular monthly member of the Surgery Residency Curriculum Committee	
9/2006 - 11/14/2007	Trauma Medical Director	
9/2006 - 11/14/2007	Chair, bimonthly Trauma Peer Review	
9/2006 - 11/14/2007	Chair, monthly Trauma/ED Conference	
9/2006 - 11/14/2007	Chair, weekly Trauma Multidisciplinary Conference and Trauma Peer Review	
9/2006-2011	Member, Operating Room Committee	
9/2006 - 11/14/2007	Quality Assurance Chair, IL Region 4 Trauma Committee	
2006-2006	Associate Director of Critical Care for Trauma Services	
7/2009-Residency Director, Department of Surgery,		
11/2012	Saint Louis University School of Medicine	
7/2009-	Member of the GME Committee of Saint Louis University School of	

11/2012	Medicine
11/2012-pres	Faculty Advisor for Surgery Resident Research
7/2017	Member of the Surgery Resident Review Committee from VA, July 2017- to present

SSM Cardinal Glennon Children's Hospital

11/14/07- 8/1/08	Interim Director of Surgery
2007-2008	Co-Director, Pediatric Trauma Services
8/2008-2011	Member of the Pediatric Trauma Committee
2007-2009	Member, Risk Management Committee
2007-2008	Chair, Trauma Peer Review Committee
11/14/07- 8/1/08	Member as the Interim Director of Surgery, Medical Executive Committee
1/2009 - 12/2011	Member as the medical staff elected <i>ad hoc representative</i> , Medical Executive Committee

Saint Louis University

9/1/2016 to Saint Louis University Service Appreciation Committee
2018 (faculty member of SLU HR Committee directing the Annual Service
Awards Recognitions presented annually in September)

Saint Louis University School of Medicine, Department of Surgery

2012 - 2020	Co-director of the Grand Rounds and Morbidity and Mortality Committee
2018 - pres	Chief, Unit II General Surgery, John Cochran (STL) VAMC
2017 - pres	Surgery Residency clinical competency committee which semi-annually reviews all General Surgery residents
2019 - pres	General Surgery VA Site Director

II. National and Regional Committees

1994-1996 Blue Cross/Blue Shield of Missouri

	Statewide Digestive Panel for Practice Guidelines
1995	Missouri State Representative to the Annual Meeting of the
	Young Surgeons of the American College of Surgeons
1996	President-elect of the St. Louis Surgical Society
1996	Education Committee, Missouri Chapter, American College of Surgeons
1996	CouncilorMissouri Chapter American College of Surgeons
1996	Slide librarian for EGD and ERCP, Society of American
	Gastrointestinal Endoscopic Surgeons (SAGES)
1996	ASGE Postgraduate Education Committee Member
1996	Member of the ACS Missouri Committee on Applicants District 1
2001	Abstract reviewer for the Chicago Surgery Society
2006-2007	Chairman, Region IV, Illinois Trauma System
2013-2015	CouncilorMissouri Chapter, American College of Surgeons
2015-2017	Vice-president, Missouri Chapter, American College of Surgeons
2017 - 2018	President, Missouri Chapter, American College of Surgeons

III. Journal Peer Reviewer

- 1. Surgical Endoscopy (~1990-2001)
- 2. Surgical Laparoscopy & Endoscopy (~1990-2001)

J. Research Support:

- 1. VA Merit Review Grant -- "Evaluation of New Methods of Proximal Gastric Vagotomy (PGV)" Three year grant (extended one additional year): October 1, 1992 September 30, 1996. \$400,000
- 2. Educational Grant for the San Joaquin General Hospital Surgery Residency from Wyeth Pharmaceuticals, December 17, 2002. \$1,200

Research Projects:

1. Hiler AM, Cederstrad S, Gill R, Brink D, Andrus CH, Wanken Z, Zawin J: The clinical presentation of *Entrobius vermicularis* as a etiologic agent of appendicitis. (A. Hiler has developed the IRB submission, submitted to the Saint Louis

University IRB Committee, and received initial IRB approval in November 2010 and has received continue annual approval.: IRB# 16927, 325 charts were reviewed by November 2011; IRB# 16927 renewed November 2011 with Dr. Andrus as PI with a total of 450 charts reviewed by September 2012; IRB# 16927 was renewed again in November 2013, 2014, 2015, 2016 with Dr. Andrus as PI). Discontinued November 2017.

- 2. Hopping J, Andrus C, Wiley E, Chen R: Is obesity a direct cause of childhood gallstone disease? IRB# 23197. Retrospective chart review of children undergoing cholecystectomy. Roughly 2/3 of the available charts have been reviewed. (Has been placed on hold, 2015)
- 3. Andrus CH, Andrus PC, Foster VE, Krishi P: Foreign Body Location and Retrieval Device. Patent Pending: Serial Number 13/605,086, submitted September 6, 2012, Attorney Docket No. 31065-32 (SLU 12-006), AT Ref No: 31065-32, U.S. Patent: 8,768,435 B2, July 1, 2014. Have participated as the faculty advisor to this project in the development of the clamp and its presentations in the SLU School of Engineering in I2P regional and national competitions. Will continue to work with the Office of Technology Development, Saint Louis University.

Faculty advisor, intellectual contributor, and facilitator in the development of Sonograb: Foreign Body Location and Retrieval Device. Patent pending—filed on Sept 6, 2012 as application serial no. 13/605,086. Inventors: Charles Hiram Andrus, Patrick Christopher Andrus, Virginia E. Foster, and Peddada Krishi. Patent submission through the Office of Technology Management, Saint Louis University. Sonograb presented in international competition, Idea to Product (I2P), Stockholm, Sweden, Nov 16-17, 2012 by Patrick Andrus (Charles Andrus, M.D., faculty advisor). Awarded 2nd prize in the Life Sciences category. Patent awarded: July 1, 2014.

- 4. Charles Harold Andrus, MHA, Charles Hiram Andrus, M.D., F.A.C.S, and Pamela B. Andrus, M.A., CCC-SP: *Mitochondrial Encephalopathy—A family case study of epileptic seizures, the ketogenic diet, and metabolic disorders.* John C. Kennell, PhD, Courtney F. Andrus, PA-C, R.D., L.D., Regina Lynch-Linsey, BS, MA eds. St. Peters, MO: Business Building Books, 2012. (In the summer and fall 2016, final stages of editing and proofing)
- 5. Andrus CH, Andrus PB: The ketogenic diet as an energy treatment of complex I deficiencies. Pediatric Research Days, SSM Cardinal Glennon Children's Hospital, SLUSOM, April 11, 2013. (Chapter 7: Charles Harold Andrus, MHA, Charles Hiram Andrus, M.D., F.A.C.S, and Pamela B. Andrus, M.A., CCC-SP: Mitochondrial Encephalopathy—A family case study of epileptic seizures, the ketogenic diet, and metabolic disorders. Kennell, Andrus, Lynch-Linsey, eds. 2016)

The following which were podium or poster presentations at the Annual MO state ACS meeting in May-June—2013, 2014, 2015, 2016, 2017, 2018, and 2019:

- 6. Khan AA, Jurgens JM, Hubble AA, Andrus CH: Thrombelastographic assessment in chronic disseminated intravascular coagulation (DIC).
- 7. Zahra A, Witte AJ, Krampert RM, Andrus CH: Coagulation management during an operation on a uremic patient.
- 8. Jasra B, Naunheim KS, Ely E, Andrus CH: Thymoma secreting ectopic parathyroid hormone concomitantly with tertiary hyperparathyroidism.
- 9. Nguyen KP, Andrus MF, Naunhiem KS, Andrus CH: Laparoscopic repair of a parahiatal hernia.
- 10. Sun Y, Williams MS, Peterson BG, Andrus CH: Acute and chronic central abdominal venous thrombosis three decades after necrotizing enterocolitis.
- 11. Gorantla K, Andrus CH, Andrus PC, Andrus CH: Crush protection due to pediatric chest wall malleability?
- 12. Sen R, Sun Y, Andrus MF, Leuhr EA, Andrus CH: Transappendiceal ileoscopy during operative reduction of an ileocolic intussusception.
- 13. Farrell KA, Salter EE, Andrus CH: The 150 Year Promise that Irrevocably Impacts Surgical Education to this Day.
- 14. Patel S, Sun A, Andrus CH: Is the Cold Appendix Acceptable in this Era of Advanced Imaging? Carlson EAJ, Sun Y, Andrus CH: Resolution of a Decade of Chronic Abdominal Pain after a Laparoscopic Incisional Hernia Repair.
- 15. Lobb Jennifer, MD, Diggs L, MD, Andrus CH: Surgical Management of AIDS/HIV Related Gastrointestinal Disease in the Modern Era: A Case Report.
- 16. LaPlante J, Glasgow S, Andrus C: Terminal ileal adenocarcinoma and synchronous renal cell CA: A Case Report.
- 17. Dwyer, Emma, Andrus CH: A forgotten chronic deficiency after a historic operation (Vitamin B12 deficiency 7 years after total gastrectomy). MO-Chapter, American College of Surgeons, 51st Annual Professional Meeting, Camden on the Lake, Lake of the Ozarks, Missouri, May 11, 2018. (Dwyer discussant: Podium presentation)
- 18. Henderson CN, Andrus CH: The evaluation and treatment of dyspepsia. MO-Chapter, American College of Surgeons, 51st Annual Professional Meeting, Camden on the Lake, Lake of the Ozarks, Missouri, May 11, 2018. (Andrus discussant: Podium presentation)

- 19. Andrus CH: Presidential Address: The ACS Pledge Relevance in the Practice of Surgery in the 21st Century. President, MO-Chapter, American College of Surgeons, 51st Annual Professional Meeting, Camden on the Lake, Lake of the Ozarks, Missouri, May 11, 2018. (Andrus discussant: Podium presentation)
- 20. Khouri AJ, Hou P, Andrus CH: Ischemic colitis in radiographic colonic lipohyperplasia: Getting it right for the wrong reason. MO-Chapter, American College of Surgeons, 52nd Annual Professional Meeting, Camden on the Lake, Lake of the Ozarks, Missouri, May 4, 2019.

Previous projects archived:

- 2002-2005. The Diversity, Epidemiology and Outcomes in Human Trauma Associated with the Livestock in an Urban/Rural County of California, IRB#02-50. A retrospective study with the accrual of approximately 75 patients. Charles Andrus, M.D., Principal Investigator; Co-investigators: Eduardo Villasenor, M.D.; Mohammed Ibrahim, M.D.; Robert Yavrouian, M.D.; Nathaniel Matolo, M.D.; Ahmed Mahmoud, M.D., faculty advisor; Colburn Ward, Ph.D.; and Ziad Ali. Initial draft of the resultant paper as of April 8, 2005-pres: Ali ZA, Andrus CH, Mahmoud A, Matolo NM, Ward CC: Don't Drink and Drive Cattle or Horses: The diversity, epidemiology and outcomes in human trauma associated with the livestock in an urban/rural county of California.
- 2. 2005-2005. ERCP during Laparoscopic Cholecystectomy, IRB #04-71. A retrospective study comparing preoperative, intraoperative, and postoperative ERCP. John Foster, M.D., Principal Investigator; Co-investigators: Hien Pham, M.D.; Charles Andrus, M.D., faculty advisor; James Bresnahan, M.D.; Ahmed Mahmoud, M.D.; Nathaniel Matolo, M.D.; Colburn Ward, Ph.D. (Data collection and some of the statistical analysis completed regarding an initial resultant paper: Andrus CH, Ali ZA, Mahmoud A, Ward CC, Matolo NM: Prospectively predicting the indications for intraoperative cholangiography during laparoscopic cholecystectomy—Should we just flip a coin?)
- 3. 2005. Severity of Injuries Sustained in Motorcycle versus Other Vehicular Accidents, #04-72. A retrospective study evaluating the severity of injury in motorcycle accidents locally in San Joaquin County responding to the research question raised when the California Highway Patrol data (1997-2001) was evaluated demonstrating twice the mortality rate among licensed motorcycle drivers vs. mortality in all other licensed vehicular accidents but a injury rate statistically identical between the two groups. Robert Keenan, M.D., Principal Investigator; Christopher Solis, M.D., Charles Andrus, M.D., faculty advisor; Nathaniel Matolo, M.D.; Colburn Ward, Ph.D.
- 4. 2005. Necrotizing Fasciitis, IRB# 04-73. A retrospective study evaluating the epidemic of necrotizing fasciitis in California mainly associated with black-tar heroin utilization and the high mortality seen in C. sordellii infections. Ronald Barbosa, M.D., Principal Investigator; Tony Chang, M.D.; Dennis Schoch, M.D.; Charles Andrus, M.D.; Nathaniel Matolo, M.D.; Ahmed Mahmoud, M.D.; Colburn Ward, Ph.D.; John E. Baker, M.D.; Hong Li, M.D.
- 5. 2005. Application to become the co-investigator for San Joaquin County, California in the multi-institutional study sponsored by the NIAID of the NIH entitled: A Phase I/II Randomized, Placebo-controlled Trial to Assess the Safety and Efficacy of Intravenous Immunoglobulin G (Omr-IgG-am™) Containing High Anti-West Nile Virus Antibody Titers in Patients with, or at High Risk for Progression to West Nile Virus (WNV) Encephalitis and/or Myelitis (CASG #210)(DMID#03-107), IRB#04-74. Richard J. Whitley, M.D., University of Alabama at Birmingham, Principal Investigator; Charles H. Andrus, M.D., F.A.C.S., local co-investigator; named collaborators with local co-investigator: Sheela Kapre, M.D., Chairperson, Dept. of Medicine, SJGH; Rod Felber, M.D., Vice-Chairperson, Dept. of Medicine, SJGH; Karen Furst, M.D., M.P.H., Health Officer, San Joaquin County Public Health Services; Dale Bishop, M.D., Assistant Health Officer, San Joaquin County Public Health Services.
- 2005. Bedside Versus Operating Room Tracheostomy, IRB#02-48. A retrospective study with the accrual of approximately 55 patients. Nathaniel Matolo, M.D., Principal Investigator; Charles Andrus, M.D., Hanlon Jen, M.D., Arvin Taneja, M.D., Samuel K.M. Liu, M.D. (Initial draft of the resultant paper as of April 8, 2005: Liu SKM, Taneja A, Jen HB, Andrus CH, Mahmoud A, Matolo N: Bedside versus operating room tracheostomy.)
- 7. 2009. Vasquez E, Ferguson K, Andrus CH: Closure of a gastrostomy site with the Carter-Thomason closure sure System: A case-report.
- 8. 2009. Grosser J, Andrus C: Preperitoneal emphysema as a cause of postoperative pain after laparoscopic appendectomy.

- 9. 2009. Aaron Llyod, M.D., Daniel Naughton, M.D., Charles Andrus, M.D., Chris Green, R.N., Pam Golden, R.N.: An epidemic of injuries found in all terrain vehicle (ATV) enthusiasts.
- 10. 2011. Andrus CH (P.I.), Aaron Scifres, M.D. (former P.I.), Christopher Aldridge, M.D., Jonathon Lusardi, MSIII, Kathryn Lindsay, Med, RN, Optimal timing of tracheostomy in severely injured elderly patients. IRB: 15975, Saint Louis University.
- 11. 2008. Luehr E, Andrus C: Transappendiceal ileoscopy during the operative reduction of intussusceptions in children.
- 12. 2008. Bailey J, Freeman C, Andrus C, other members of the SLU trauma service: Referral patterns of trauma patients to a bi-state Level I trauma service.
- 13. 2011. Andrus C, TBA: Bilateral traumatic pneumatoceles after a rapid acceleration/deceleration crushing chest injury.

K. Bibliography:

- I. Papers published, in press, or accepted for publication in peer reviewed journals
 - 1. Gruhn TA, Benton EV, Andrus CH: The etching of cellulose nitrate plastic. Nucl Instr Methods 119:131-133, 1974.
 - 2. Andrus CH, Kaminski DL: Segmental hepatic resection utilizing the ultrasonic dissector. Arch Surg 121:515-521, 1986.
 - 3. Andrus CH, Doering M, Herrmann VM, Kaminski DL: Planned reoperation for generalized intra-abdominal infection. Am J Surg 152:682-686, 1986.
 - 4. Schlarman DE, Beinfeld MC, Andrus CH, Kaminski DL: Effects of somatostatin on acute canine experimental pancreatitis. Int J Pancreatology 2:247-255, 1987.
 - 5. Andrus CH, Ponsky JL: The effects of irrigant temperature in upper gastrointestinal hemorrhage: A requiem for iced saline lavage. Am J Gastroenterol 82:1062-1064, 1987.
 - 6. Vernava AM, Andrus CH, Herrmann VM, Kaminski DL: Pancreatitis after biliary tract surgery. Arch Surg 122:575-580, 1987.
 - 7. Andrus CH, Ponsky JL: Bezoars: Classification, pathophysiology and treatment. Am J Gastroenterol 83:476-478, 1988.
 - 8. O'Loughlin KC, Andrus CH, Kaminski DL: A simplified technique for the extirpation of the gastric bubble utilizing an endo-overtube. Am Surg 55:116-118, 1989.
 - 9. Komenda G, Andrus CH: Infection following total hip arthroplasty. VA Pract 6:43-51, 1989.
 - 10. Andrus CH, Swensson EE, Peterson GJ, Vernava AM, Langsfeld M: Pancreatic necrosis and abscess following rupture of an abdominal aortic aneurysm. Vascular Reports (Accepted 1986 and publication pending).
 - 11. Westfall SH, Andrus CH, Naunheim KS: A reproducible, safe jejunostomy replacement technique by a percutaneous endoscopic method. Am Surg 56:141-143, 1990.
 - 12. Andrus CH, Dean PA, Ponsky JL: Evaluation of safe, effective, intravenous sedation for utilization in endoscopic procedures. Surg Endosc 4:179-183, 1990.
 - 13. Shapiro MJ, Alexander AJ, Andrus CH: Gallstones in the pancreatic duct: Endoscopic retrograde pancreatographic demonstration. J Clin Gastroenterol 12(4):454-6, 1990.
 - 14. Kaminski DL, Andrus CH, German D, Deshpande YG: The role of prostanoids in the production of acute acalculous cholecystitis by platelet-activating factor. Ann Surg 212:455-461, 1990.

- 15. Larsen F, Schlarman D, Andrus C, Kaminski D: The effect of the CCK receptor antagonist CR 1409 on bile reflux pancreatitis in the opossum. Pancreas 6:291-297, 1991.
- 16. Blatner M, Wittgen CM, Andrus CH, Kaminski DL: Cystic duct cholangiography during laparoscopic cholecystectomy. Arch Surg 126:646-649, 1991.
- 17. Westfall S, Andrus C, Schlarman D, and Kaminski DL: The effect of CCK-receptor antagonists on CCK stimulated bile flow in dogs. Surg 109:294-300, 1991.
- 18. Wittgen CM, Andrus CH, Fitzgerald SD, Baudendistel LJ, Dahms TE, Kaminski DL: Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. Arch Surg 126:997-1001, 1991.
- 19. Andrus CH: Endoscopic ultrasonography: A new highly sensitive and specific diagnostic and staging technique for upper gastrointestinal tumors. Saint Louis Metro Medicine 13:21-23, 1991.
- 20. Andrus CH, Daly JL: Evaluation of Surgical Services in a Large University-Affiliated VA Hospital: Use of an In-House-Generated Quality Assurance Data Base. So Med J 84:1447-1450, 1991.
- 21. Schneider T, Fitzgerald S, LaRegina M, Kaminski D, Andrus C: Evaluation of proximal gastric vagotomy by cobaltous chloride (COCl2) chemoneurolysis in a rat model. ACS Surgical Forum XLII:177-179, 1991.
- 22. Fitzgerald SD, Bailey PV, Liebscher GJ, Andrus CH: Laparoscopic cholecystectomy in anti-coagulated patients. Surg Endosc 5:166-169, 1991.
- 23. Fitzgerald SD, Andrus CH, Baudendistel LJ, Dahms TE, Kaminski DL: Hypercarbia during carbon dioxide pneumoperitoneum. Am J Surg 163:186-190, 1992.
- 24. Schneider TA, Andrus CH: The endoscopic Congo red test during proximal gastric vagotomy: an essential procedure. Surg Endosc 6:16-17, 1992.
- 25. Schneider TA, Andrus CH: The endoscopic Congo red test during proximal gastric vagotomy: an essential procedure. (The Authors Reply). Surg Endosc 7:210, 1993.
- 26. Parra RO, Andrus CH, Boullier JA: Staging laparoscopic pelvic lymph node dissection: Comparison of results with open pelvic lymphadenectomy. J Urol 147:875-878, 1992.
- 27. Hagood PG, Mehan DJ, Worischeck JH, Andrus CH, Parra RO: Laparoscopic varicocelectomy: Preliminary report of a new technique. J Urol 147:73-76, 1992.
- 28. Naunheim KS, Petruska PJ, Roy T, Andrus CH, Johnson FE, Schlueter JM, Baue AE: Preoperative chemoradiation and radiotherapy for esophageal carcinoma. J Thorac Cardiovasc Surg 103:887-895, 1992.

- 29. Parra RO, Jones JP, Andrus CH, Hagood PG: Laparoscopic diverticulectomy: Preliminary report of a new approach for the treatment of bladder diverticulum. J Urol 148:869-871, 1992.
- 30. Parra RO, Andrus CH, Jones JP, Boullier JA: Laparoscopic cystectomy: Initial report on a new treatment for the retained bladder. J Urol 148:1140-1144, 1992.
- 31. Parra RO, Andrus CH, and Boullier JA: Staging laparoscopic pelvic lymph node dissection: experience and indications. Arch Surg 127:1294-1297, 1992.
- Wade TP and Andrus CH: Cardiorespiratory effects of laparotomy in patients with spinal cord injury. Am Surg 59:689-691, 1993.
- 33. Wade TP, Jewell WR, Andrus CH: Mesenteric venous thrombosis. Surg Endosc 6:283-284, 1992.
- 34. Schneider TA, Wittgen CM, Andrus CH, Kaminski DL: Comparison of minimally invasive methods of parietal cell vagotomy in a porcine model. Surg 112:649-655, 1992.
- 35. Wittgen CM, Andrus JP, Andrus CH and Kaminski DL: Cholecystectomy: Which procedure is best for the high-risk patient. Surg Endosc 7(5): 395-399, 1993.
- 36. Mehan DJ, Andrus CH, Parra RO: Laparoscopic internal spermatic vein ligation: report of a new technique. Fertility and Sterility 58:1263-1266, 1992.
- 37. Mehan DJ, Andrus CH, and Parra RO: Simultaneous laparoscopic varicocelectomy and removal of an intrascrotal atrophic testicle. Surgical Laparoscopy & Endoscopy 2(4):327-331, 1992.
- 38. Wade TP, Kaminski DL, Andrus CH: Evaluations of surgery resident performance correlate with success in board examinations. Surgery 113:644-648, 1993.
- 39. Wittgen CM, Schneider TA, Fitzgerald SD, Panneton WM, LaRegina MC, Johnson S, Kaminski DL, Andrus CH: Proximal gastric vagotomy by minimally invasive methods in an acute rat model. Surg Endosc 7:319-324, 1993.
- 40. Wittgen CM, Naunheim KS, Andrus CH, Kaminski DL: Preoperative pulmonary function evaluation for laparoscopic cholecystectomy. Arch Surg 128:880-886, 1993.
- 41. Naunheim KS, Andrus CH: Thoracoscopy resection of giant mediastinal cyst. Ann Thor Surg 55:156-158, 1993.
- 42. Andrus CH: Invited Commentary, "Hemodynamic Effects of Argon Pneumoperitoneum." [comment] Surg Endosc 8:322-323 1994.
- 43. Neuberger TJ, Wittgen CM, Schneider TA, Andrus CH, Panneton WM, Kaminski DL: Evaluation of alternative proximal gastric vagotomy technique after a nine-month interval in a rat model. Gastroenter Endosc 40:316-320, 1994.
- 44. Andrus CH: Endoscopic assessment of vascular disorders. Sem Colon Rect Surg 5:27-31, 1994.

- 45. Votapka TV, Pennington DG, McBride LR, Kaminski DL, Andrus CH, Swartz MT: Non-cardiac surgery in patients supported with mechanical circulatory support devices: A report of seven cases. J Am Coll Surgeons 179:318-320, 1994.
- 46. Wade TP, Comitalo JB, Andrus CH, Goodwin MM, Kaminski DL: Laparoscopic cancer surgery: Lessons from gallbladder cancer. Surg Endosc 8:698-701, 1994.
- 47. Kurzweil SM, Shapiro MJ, Andrus CH, Wittgen CM, Herrmann VM, and Kaminski DL: Hyperbilirubinemia without common duct abnormalities and hyperamylasemia without pancreatitis in patients with gallbladder disease. Archives of Surgery 129:829-833, 1994.
- 48. Andrus CH: Letter to the Editor: Exploratory laparoscopy for perforation following colonoscopy (4:241-3, 1994). Surg Laparosc Endosc 4:327, 1994.
- 49. Marts BC, Carr SC, Andrus CH, Kaminski DL, Wade TP: Staged surgical management of cholecystocutaneous abscess. Contemp Surg 45:273-277, 1994.
- 50. Andrus CH, Wittgen CM, and Naunheim KS: Anesthetic and physiological changes during laparoscopy and thoracoscopy: The surgeon's view. Seminars in Laparoscopic Surgery 1:228-240, 1994.
- 51. Parra RO, Hagood PG, Boullier JA, Cummings JM, Mehan DJ: Complications of laparoscopic urological surgery: Experience at Saint Louis University. J Urol 151:681-684, 1994.
- 52. Ure T, Dehghan K, Vernava III AM, Longo WE, Andrus CA, Daniel GL: Colonoscopy in the elderly. Surg Endosc 9:505-508, 1995.
- 53. Silen ML, Canvasser DA, Kurkchubasche AG, Andrus CH, and Naunheim KS: Video-assisted thoracic surgical repair of a foreamen of Bochdalek hernia. Ann Thorac Surg 60:448-450, 1995.
- 54. Wibbenmeyer LA, Wade TP, Chen RC, Turgeon RP, Meyer RC, Andrus CH: Laparoscopic cholecystectomy can disseminate in-situ gallbladder cancer. J Am Col of Surg 181:504-510, 1995.
- 55. Neuberger TJ, Andrus CH, Wittgen CM, Wade TP, Kaminski DL: Prospective comparison of helium versus carbon dioxide pneumoperitoneum. Gastrointestinal Endoscopy 43:38-41, 1996.
- 56. Naunheim KS, Landreneau RJ, Andrus CH, Ferson PF, Zachary PE, Keenan RJ: Laparoscopic fundoplication: A natural extension for the thoracic surgeon. Ann Thorac Surg 61:1062-1065, 1996.
- 57. Warner PM, Andrus CH: Hemodynamic and pulmonary implications and complications in laparoscopic surgery. Sem Laparoscopic Surg 4:135-138, 1997.
- 58. Wade TP, Feldman MS, Andrus CH: The spectrum of mucus-secreting pancreatic neoplasia. Am J Gastroenterol 92:154-155, 1997.

- 59. Damore LJ, Andrus CH, Herrmann VM, Wade TP, Kaminski DL, Kaiser GC: Prospective evaluation of a new through-the-scope nasoduodenal enteral feeding tube. Surg Endosc 11:460-463, 1997.
- 60. El-Ghazzawy AG, Gupta N, Swope TJ, Kulkarni AD, Panneton WM, Robinson SM, Niehoff ML, Kaminski DL, Andrus CH: Evaluation of benzalkonium chloride chemoneurolytic proximal gastric vagotomy. Surg Endosc 12:207-211, 1998.
- 61. Andrus CH, Cosgrove JM, Longo WE, eds. *Minimally Invasive Surgery: Principles and Outcomes*. Amsterdam, Harwood Academic Publishers, July, 1998.
- 62. Soweid AM, Clarkston WK, Andrus CH, Janney CG: Diagnosis and management of appendiceal mucoceles. Dig Dis 16:183-186, 1998.
- 63. Andrus CH, Johnson K, Pierce E, Romito PJ, Hartel P, Berrios-Guccione S, Best W: Finance modeling in the delivery of medical care in tertiary care hospitals in the Department of Veterans Affairs. J Surg Res 96:152 -157, 2001.
- 64. Kleinman B, Baumann M, Andrus C: Faulty design resulting in temporary pacemaker failure. Chest 120:684-685, 2001.
- 65. Andrus CH, Villasenor EG, Kettelle JB, Roth R, Sweeney AM, Matolo NM: "To Err is Human": Uniformly Reporting Medical Errors and Near Misses: A Naïve, Costly and Misdirected Goal. J Am Coll Surg 196(6): 911-918, June 2003. [Was requested on January 29, 2004 by Doris Goldstein, M.L.S., M.A., Director, National Reference Center for Bioethics Literature for inclusion in the collection of published bioethical articles of the Joseph and Rose Kennedy Institute of Ethics, Georgetown University, National Reference Center for Bioethics Literature supported by the U.S. National Library of Medicine. Added to the library's "ETHX on the Web" at http://bioethics.georgetown.edu in August, 2004.]
- 66. Mahmoud A, Andrus CH, Matolo NM, Ward CC: Directed postgraduate study result in quantitative improvement in ABSITE scores. Am J Surg 191;812-816, 2006.
- 67. Leon L, Labropoulos N, Hudlin CI, Macbeth AG, Matolo N, Andrus CH: Accessory Spleen Rupture in a Patient with Previous Traumatic Splenectomy. J Trauma 60:901-903, 2006.

II. Book chapters:

- 1. Drucker WR, Foster RS, Gamelli RL, et al.: Clinical Surgery (Andrus -- one of several surgical resident editors) (St. Louis: C.V. Mosby, 1987).
- 2. Andrus CH, Kaminski DL: Specialized Therapeutic Considerations for Patients with Hepatobiliary Disease. Essentials of Clinical Hepatology. Gholson CF, Bacon BR editors. Mosby, 1992, St. Louis, pp. 134-154.

- 3. Andrus CH and the Missouri Statewide Practice Guidelines for Digestive Conditions Committee: Practice Guidelines: Digestive. Alliance, BlueCross BlueShield, 1995.
- 4. Andrus CH: Set up of the Operating Suite and Instrumentation for Laparoscopy. In: Parra RO, Boullier, JA (eds.). Urologic Laparoscopic Surgery. McGraw Hill, Inc., Blacklick, Ohio, 1995.
- 5. Andrus CH, Wittgen CM, Parra RO: Physiologic and Anesthetic Principles of Laparoscopy. In: Parra RO, Boullier JA (eds.). Urologic Laparoscopic Surgery. McGraw Hill, Inc., Blacklick, Ohio, 1995.
- 6. Andrus CH: Pneumoperitoneum during urologic laparoscopy. In: Parra RO, Boullier JA (eds.). Urologic Laparoscopic Surgery. McGraw Hill, Inc., Blacklick, Ohio, 1995.
- 7. Andrus CH, Naunheim KS, Wittgen CM: Anesthetic considerations. In: MacFadyen BV, Ponsky JL (eds.): Operative Laparoscopy & Thoracoscopy. Lippincott-Raven, Philadelphia, PA, 1996.
- 8. Laureano BA, Andrus CH, Kaminski DL. Cardiovascular changes during laparoscopy. In: Rosenthal RJ, Friedman RL, Phillips EH. The pathophysiology of pneumoperitoneum. New York: Springer; 1991, pp. 77-84.
- 9. Deveaux PG, Andrus CH: Minimally Invasive Surgery in the Immunocompromised Patient. Minimally Invasive Surgery: Priniciples and Outcomes. CH Andrus, JM Cosgrove, WE Longo, eds. Amsterdam, Harwood Academic Publishers, July, 1998, pp. 377-380.
- 10. Chough EK, Andrus CH: Physiology of Pneumoperitoneum. Minimally Invasive Surgery: Priniciples and Outcomes. CH Andrus, JM Cosgrove, WE Longo, eds. Amsterdam, Harwood Academic Publishers, July, 1998, pp. 13-18.
- 11. Andrus CH, Miller SH: Small Bowel Enteroscopy. The SAGES Manual: Fundamentals of Laparoscopy and GI Endoscopy. Carol Scott-Conner, editor. Springer-Verlag, New York, NY, 1998, pp. 480-484.
- 12. Schaffner J, Andrus CH: GI Bleeding. Multidisciplinary Critical Care Board Review Course. Society of Critical Care Medicine, July, 1998, pp. 127-137.
- 13. Napolitano M, Andrus CH: Preoperative and Postoperative Care of the Flexible Endoscopy Patient. Mastery of Endoscopic and Laparoscopic Surgery, eds.: W.Stephen Eubanks, Lee L. Swanstrom, Nathaniel J. Soper. (Philadelphia: Lippincott Williams & Wilkins, 1999), pp. 12-17.
- 14. Andrus CH, Miller SH: Chapter 59: Small Bowel Enteroscopy. The SAGES Manual: Fundamentals of Laparoscopy and GI Endoscopy, Second Edition. Carol Scott-Conner, M.D., F.A.C.S., editor. Springer-Verlag, New York, NY, 2006.

III. Abstracts

- 1. O'Loughlin KC, Andrus CH, and Kaminski DL: A simplified technique for the extirpation of the gastric bubble utilizing an endo overtube. Am Surg 54:526, 1988.
- 2. Andrus CH, Dean PA, Ponsky JL: Evaluation of safe effective intravenous sedation for utilization in endoscopic procedures. Surg Endosc 4:56, 1990.
- 3. Vernava AM, Beckman R, Andrus C, Johnson F, Herrmann V, Kaminski DL: Tangential colostomy preferred for temporary fecal diversion. Dis Colon Rectum 33(3):26, 1990.
- 4. Vernava AM, Doering M, Andrus C, Johnson F, Herrmann V, Kaminski D: Flow cytometry in colorectal cancer. So Med J, pp. 2S-11, 1990.
- 5. Andrus CH, Daly JL: Utilization of an in-house generated quality assurance database for the evaluation of the surgical services in a large university-affiliated VA hospital. So Med J, pp. 2S-79, 1990.
- 6. Mehan DJ, Hagood PG, Worischeck JH, Andrus CH, and Parra R: Laparoscopic varicocelectomy: Preliminary report of a new technique, Part I. J Urol 145:242A, #117, 1991.
- 7. Boullier JA, Andrus CH, Parra RO: Staging laparoscopic pelvic lymph node dissection, initial report. J Urol 145:423A, #841, 1991.
- 8. Hagood PG, Mehan DJ, Worischeck JH, Andrus CH, Parra RO: Laparoscopic varicocelectomy. (Video). J Urol 145:204A, #V-51, 1991.
- 9. Andrus CH, Wittgen CM, Naunheim KS, McManama GP, Rinehart GC, Clarkson WK, Wade TP: Densitometric evaluation of endoscopic ultrasonography. Gastrointest Endosc 38:271-272, 1992.
- 10. Wittgen CM, Andrus JP, Andrus CH, Kaminski DL: Cholecystectomy: Which procedure is best for the high risk patient? Surg Endosc 6:88, 1992.
- 11. Petruska P, Naunheim K, Roy T, Andrus C, Johnson F, Daniel F, Spencer L, Baue A: Preoperative chemoradiation for esophageal carcinoma. Proc ASCO 11:182, 1992.
- 12. Schneider TA, LaRegina MC, Fitzgerald SD, Wittgen CM, Virgo KS, Kaminski DL, Andrus CH: Confirmation of parietal cell distribution by histologic and Congo red techniques in a porcine model. Gastroenterology 102:A161, 1992.
- 13. Wittgen CM, Neuberger TJ, Schneider TA, Andrus CH, Panneton WM, Kaminski DL: Evaluation of alternate PGV techniques in a chronic rat model. Gastrointestinal Endoscopy 39 (2)269.
- 14. Beckman R, Andrus C, Johnson F, Herrmann V, Kaminski D: Colostomy formation and closure. Proc Mo Chapt Am Coll Surg 21:17, 1988.
- 15. Neuberger TJ, Andrus CH, Wittgen CM, Wade TP, Kaminski DL: Prospective comparison of helium versus carbon dioxide pneumoperitoneum.

 Gastrointestinal Endoscopy 40:P30, 1994.

- 16. Marts BC, Carr SC, Andrus CH, Kaminski DL, Wade TP: Staged surgical management of cholecystocutaneous abscess. Contemporary Surgery 45(5):273-277, 1994.
- 17. Damore LJ, Andrus CH, Herrmann VM, Wade TP, Kaminski DL, Kaiser GC: Prospective evaluation of a new through-the-scope nasoduodenal enteral feeding tube. S162 Surg Endosc 10: 212, 1996.
- 18. El-Ghazzawy AG, Gupta N, Swope TJ, Kulkarni AD, Panneton WM, Robinson SM, Niehoff ML, Kaminski DL, Andrus CH: Evaluation of benzalkonium chloride chemoneurolytic proximal gastric vagotomy. Surg Endosc 11:196, 1997. (Abstract & Poster, SAGES, March, 1997)
- 19. Andrus CH, Miller GA, Sunwoo YC, Nowlin LJ, Millis BM, Ellison JA, Qualls C, Johnson FE: The quality assurance evaluation of an abdominal wound evisceration epidemic!? Poster Southwestern Surgical Congress, April, 1997.
- 20. Zapotocky T, Heintz-Miller K, Brayshaw M, Foley S, Lau MT, Byrne R, Andrus CH: A comparison of foley catheters as feeding tubes versus standard gastrostomy tubes. Poster N0044, ASPEN, 25th Clinical Congress, Chicago, IL, January 21-24, 2001.
- 21. Foley, S, Clemmer M, Martling W, Williams D, Heintz-Miller K, Lau MT, Byrne R, Andrus CH, Reinhardt G: Hypoalbuminemia and mortality in a hospitalized veteran population: Comparison over 20 years. Poster N0014, ASPEN, 25th Clinical Congress, Chicago, IL, January 21-24, 2001.
- 22. Andrus CH, Kleinman BS, Mozdzierz G, Sinacore JM, Garthwaite TA: Mortality outcomes and attending surgeon presence at the time of operation. Submitted November 15, 2002 for consideration for presentation at the 23rd Annual Meeting of the Association for Surgical Education, Vancouver, B.C., Canada, May 6-8, 2003. Accepted for podium presentation for May 7, 2003.
- 23. Andrus CH, Mozdzierz GJ, Mahmoud AM, Kettelle JB, Matolo NM: "Primum Non Nocere" vs. "the Bottom-line" in Surgical Education: Submitted December 3, 2002 for consideration for presentation at the Annual Meeting of the Association of Program Directors in Surgery, Vancouver, B.C., Canada, May 6-8, 2003. Rejected January, 2003.
- 24. Vasquez E, Scifres A, Lindsay K, Bailey J, Freeman C, Andrus C. Utilization in the treatment of victims of traumatic cardiopulmonary arrest. Submitted to Missouri Chapter of American College of Surgeons, April 2007.

L. Current and past teaching responsibilities:

- 1. Andrus CH: Indications and uses for flexible sigmoidoscopy in the family practice office: Illinois Academy of Family Physicians, St. Elizabeth's Hospital. Belleville, IL, October 29, 1987.
- 2. Andrus CH, Herrmann V: Total enteral nutrition. Staff of Grand Island VAH, Grand Island, NE, December 3, 1987.
- 3. Andrus CH: Selection of appropriate enteral feeding tubes. ASPEN, St. Louis, MO, September 8, 1988.

- 4. Andrus CH: Endoscopically placed feeding tubes: indications and methods. ASPEN, St. Louis, MO, September 9, 1988.
- 5. Andrus CH: The physician's role in the hyperalimentation team. RMEC. Saint Louis VAMC, St. Louis, MO, April 12, 1989.
- 6. Andrus CH, Wittgen CM: Advances in laparoscopic diagnosis and therapy. Gastroenterology Grand Rounds, Saint Louis University, October 13, 1989.
- 7. Andrus CH: Advances in surgical endoscopy "Away From Winter-1990", Saint Louis University, St. Louis, MO, February 11, 1990.
- 8. Andrus CH: AIDS and the health care worker. Labor Health Institute Staff, Saint Louis, MO, April 26, 1990.
- 9. Andrus CH: Surgical endoscopy. St. Joseph's Hospital Surgical Staff, Saint Joseph's Hospital, St. Louis, MO, May 23, 1990.
- 10. Andrus CH: Laparoscopy and the general surgeon. Lab demonstrations of laparoscopic cholecystectomy. St. Mary's Health Center, St. Louis, MO, June 9, 1990.
- 11. Andrus CH: Cholangiography during laparoscopic cholecystectomy. Lab demonstration of laparoscopic cholecystectomy. Mt. Sinai Medical Center, Cleveland, OH, July 6-7, 1990.
- 12. Andrus CH: Advances in laparoscopic surgery. Gastroenterology Grand Rounds, Saint Louis University, November 28, 1990.
- 13. Andrus CH: Biliary tract and pancreatic duct emergencies. Emergency Department Grand Rounds, Saint Louis University, December 11, 1990.
- 14. Andrus CH, Andrus PB, Daake C: Stress ulcers in critically ill patients. Annual Meeting of the Greater St. Louis Chapter of the American Association of Critical Care Nurses, St. Louis, MO, March 15, 1991.
- 15. Andrus CH, Vernava AM: Laparoscopy: Are there any indications in colorectal disease? "Management of colon and rectal disease in 1991: An update for the practitioner, specialist, and surgeon," Saint Louis University, April 20, 1991.
- 16. Andrus CH, Soper N: Laparoscopic surgery: Point/counterpoint. Surgical Grand Rounds at Saint Louis University, September 28, 1991.
- 17. Andrus CH: Endoscopic ultrasonography. Annual meeting of GSGNA (Gateway Society of Gastroenterology, Nurses and Associates) at Christian Northeast Hospital, St. Louis, MO, October 26, 1991.
- 18. Andrus CH, Fleshman J, Vernava AM, Wexner S: Laparoscopic colectomy: The future is here? "Management of challenging problems in colon and rectal disease in 1992: An update for the clinician," Saint Louis University, April 25, 1992.
- 19. Andrus CH: An overview of laparoscopic surgery. Founders Week Scientific Program--Medical Alumni, Saint Louis University, October 23, 1992.

- 32
- 20. Andrus CH: What is new in laparoscopy? General Grand Rounds, Saint Elizabeth's Hospital, Belleville, IL, October 27, 1992.
- 21. Andrus CH: What's new in laparoscopy? Monthly meeting of the St. Louis Chapter of the Occupational Health Nurses Association, Westport Plaza, St. Louis, MO, January 28, 1993.
- 22. Andrus CH: Dietary modification in the treatment of inborn errors in metabolism. Freshman medical student nutrition course, Saint Louis University Medical School, April 22, 1993.
- 23. Andrus Charles Hiram and Andrus Charles Harold: Clinical Case Study: Dietary modifications in the treatment of childhood epilepsy. Freshman medical student nutrition course, Saint Louis University Medical School, April 22, 1993, April 19, 1994, April, 1995, & April 4, 1996.
- 24. Andrus CH: An infectious cause of peptic ulcer disease: Helicobacter pylori. Weekly Transplant Grand Rounds, Saint Louis University Hospital, May 26, 1993.
- 25. Andrus CH: Endoscopic assessment of ischemic colitis. Surgery/Gastroenterology Combined Rounds, Saint Louis University Hospital, June 2, 1993.
- 26. Andrus CH: Hepatic failure. St. Louis VAMC Critical Care Course for Nurses. John Cochran VAMC, St. Louis, MO, September 3, 1993, September 22, 1995, November 17, 1995, February 16, 1996.
- 27. Andrus CH: Indications for upper endoscopy. SAGES Endoscopy Workshop for Surgical Residents. Ethicon Endo-Surgery Institute, Cincinnati, Ohio, January 21-22, 1994, January 13-14, 1995.
- 28. Andrus CH: Physiologic effects of pneumoperitoneum. St. John's Mercy Medical Center, August 10, 1994.
- 29. Andrus CH: The Abdomen and Nutrition. Practical Anatomy and Surgical Technique Workshop of St. Louis, November 9, 1994.
- 30. Andrus CH: Health Options for Teens. Saint Louis University Hospital in conjunction with the American Lung Association. St. Louis, MO, July 11, 1995.
- 31. Andrus CH: The Acute Abdomen. Internal Medicine Resident Conference. Saint Louis University Medical Center. July 20, 1995.
- 32. Andrus CH: What's new in laparoscopy? Grand Rounds, Saint Louis University Medical Center, January 27, 1996.
- 33. Andrus CH: Physiological changes during laparoscopy. Grand Rounds, Saint Louis University Medical Center, February 28, 1996.
- 34. Andrus CH: The indications of upper endoscopy and the therapeutic maneuvers in esophageal stricture disease and peptic ulcer disease. M&M Group I (Blue, Vascular, VAH, C/R), Saint Louis University Medical Center, April 10, 1996.
- 35. Andrus CH: Ethicon endosurgery resident laparoscopic training program. Saint Louis University Medical Center, June 21-22, 1996.

- 36. Andrus CH: Molecular biology in this era of managed care. Department of Surgery Grand Rounds, Loyola University Medical School, October 19,1996.
- 37. As the former President-elect of the St. Louis Surgical Society, I coordinated the St. Louis Surgical Society's Fall Panel of November 5, 1996, on: "Molecular Medicine and the Practicing Surgeon" which included the discussants: Robert Smith, M.D., Ph.D., Professor of Medicine, Joslin Diabetic Clinic, Harvard University: "An Overview of Molecular Biology and its Influences on Clinical Practice"; Diane Radford, M.D., F.A.C.S., Assistant Professor of Surgery, Washington University School of Medicine: "Genetic Screening in Breast Malignancies"; Charles Andrus, M.D., F.A.C.S.: "Molecular Biology and Managed Care"; and Kevin O'Rourke, O.P., J.C.D., Saint Louis University School of Medicine: "The Ethical Implications of Molecular Biological Diagnoses and Therapy."
- 38. Andrus CH: What's new in laparoscopy. Department of Surgery Grand Rounds, Loyola University Medical School, January 11, 1997.
- 39. Andrus CH: What's new in laparoscopy. GI Service Conference, Edward Hines, Jr. VAH, May 21, 1997.
- 40. Andrus CH: As a Chemistry major, you want to be a doctor? Loyola University Chapter of the American Chemical Society, Loyola University, Lakeshore Campus, November 30, 1999.
- 41. Andrus CH: Laparoscopic staging of pancreatic cancer. Tumor Board conference: "The Role of Imaging in the Staging of Pancreatic Cancer." Loyola University Medical Center, April 11, 2001.
- 42. Andrus CH: Medical Implications of MVAs. To the Driver Education Classes of St. Mary's High School, Stockton, CA. November 6, 2002.
- 43. Andrus CH: Transfusion therapy. Surgery Residents, San Joaquin General Hospital, January, 2003.
- 44. Andrus CH: Transfusion therapy. Combined Pathologic Conference (Departments of Family Practice, Internal Medicine, & Surgery), San Joaquin General Hospital, July 30, 2003.
- 45. Andrus CH: Presentation to SJGH Surgical Grand Rounds: S A F E R: Sleep, Alertness, and Fatigue Education in Residency, September 24, 2003.
- 46. Andrus CH: MVAs: The Silent Epidemic of Youthful Drivers. The presentation by the Medical Director, Trauma Services, SSM DePaul Health Center, on the two day MADD-sponsored docudrama. Ritenour High School, St. John, MO, May 6, 2005.
- Andrus CH: Trauma and the Pregnant Patient. Lecture Series for Emergency Medical Services, St. Louis County Fire Districts, as co-Director, EMS Services, SSM DePaul Health Center, St. Louis, MO June 1-3, 2005. 6 presentations x 2 hrs = 12 hours of presentations.
- 48. Andrus CH, Scodary D: Head Trauma. Lecture Series for Emergency Medical Services, St. Louis County Fire Districts, as co-Director, EMS Services, SSM DePaul Health Center, St. Louis, MO September 20-22, 2005. 6 presentations x 2 hrs = 12 hours of presentations.

- 49. Andrus CH: Trauma Classification and EMS/ED Communications Lecture Series for Emergency Medical Services, St. Louis County Fire Districts, as co-Director, EMS Services, SSM DePaul Health Center, St. Louis, MO November 16-18, 2005. 9 presentations x 2 hrs = 18 hours of presentations.
- 50. Andrus CH: From the Accident Scene to the ED via the Back Board. Lecture Series for Emergency Medical Services, St. Louis County Fire Districts, as co-Director, EMS Services, SSM DePaul Health Center, St. Louis, MO March 7-9, 2006. 9 presentations x 2 hrs = 18 hours of presentations.
- 51. Andrus CH: Combating a Major Killer. Presentation in conjunction with DocuDrama at Pattonville High School on Drunk Driving, April 12, 2006.
- 52. Andrus CH: Abdominal Trauma: The Silent Killer. Lecture Series for Emergency Medical Services, St. Louis County Fire Districts, as co-Director, EMS Services, SSM DePaul Health Center, St. Louis, MO April 18-20, 2006. 9 presentations x 2 hrs = 18 hours of presentations.
- 53. Andrus CH, O'Connor M: Impediments to the Delivery of Trauma Care at SSM DePaul Health Center. Presented before the public portion of the SSM DePaul Health Center Trauma Peer Review Committee, June 12, 2006.
- 54. Andrus CH: Acute abdomen and appendicitis. Junior medical student lectures every cycle. Department of Surgery, Saint Louis University School of Medicine.
- 55. Andrus CH: Hernia. Junior medical student lectures every cycle. Department of Surgery, Saint Louis University School of Medicine.
- 56. Andrus CH: Small bowel obstruction. Junior medical student lectures every cycle. Department of Surgery, Saint Louis University School of Medicine.
- 57. Andrus CH: Accountability, AMDG, Surgical Education, and One Surgeon's View.
 Surgery Grand Rounds, Saint Louis University University School of Medicine, October 18, 2006.
- 58. Andrus CH: To Err is Human-Surgical Self-Reflection as a Tradition: The M&M Conference. Surgery Grand Rounds, Saint Louis University School of Medicine, March 28, 2007.
- 59. Andrus CH: Appendicitis, Acute Abdomen, Small Bowel Obstruction, and Hernias.

 Lecturer to the junior class of every junior student surgery rotation six to eight times a year.
- 60. Andrus CH: Andrus PB, Andrus CH, Andrus PC, Andrus TM, Andrus MF, Andrus TS: The Story of a Mitochondrial Cytopathy A Case Study in Molecular Biology. Freshman Molecule Biology Course, Saint Louis University School of Medicine, October 30, 2007.
- 61. Andrus CH: Mitochondrial Cytopathies: Mysteries Wrapped in Enigmas One Family's Experience, St. Louis University Pediatric Grand Rounds, SSM Cardinal Glennon Children's Medical Center, September 24, 2008; St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, October 1, 2008; and St. Louis University Obstetrics & Gynecology Grand Rounds, SSM St. Mary's Health Center, October 3, 2008.

- 62. Andrus CH: Pediatric Trauma, State of Illinois Trauma Nurse Specialist Program, St. Louis University Hospital, February 20, 2009 and March 13, 2009.
- 63. Andrus CH: The Surgery Resident On-Call: A Potpourri of Perioperative Care and Challenges. St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, March 25, 2009.
- 64. Andrus CH: The PIF. Saint Louis University Surgery Grand Rounds, St. Louis University School of Medicine, June 3, 2009.
- 65. Andrus CH: 2009 2010 Resident Orientation. Department of Surgery, Saint Louis University School of Medicine, June 30, 2009.
- 66. Andrus CH: Surgery Residency in 2009. Saint Louis University Surgery Grand Rounds, St. Louis University School of Medicine, June 24, 2009.
- 67. Andrus CH: Stress, Fatigue, and the IOM report: *Resident Duty Hours Enhancing Sleep, Supervision, and Safety*. Saint Louis University Surgery Grand Rounds, St. Louis University School of Medicine, August 5, 2009.
- 68. Andrus CH: Basic Science: The Adrenal Gland Anatomy, physiology, and syndromes / functional pathology. Saint Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, September 2, 2009.
- 69. Andrus CH: The Changing Facets of Postgraduate Surgical Education. Saint Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, September 16, 2009.
- 70. Klinkner DB, Andrus CH: Basic Science: Adrenal Gland II--Pathologic Conditions, Operations, and Chemical Therapies, Saint Louis University Surgery Grand Rounds, St. Louis University School of Medicine, September 23, 2009.
- 71. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, October 1, 2009.
- 72. Andrus CH and other Trauma Surgery Faculty: "Trauma Jeopardy", Department of Surgery Grand Rounds, December 16, 2013.
- 73. Andrus CH: Instructor, ATLS Course, Course #35374-P, Saint Louis University Hospital, January 22, 2010.
- 74. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, January 28, 2010.
- 75. Andrus CH: Surgical Residency: Roles, Responsibilities, and Relationships, Department of Surgery Grand Rounds, Saint Louis University School of Medicine, February 3, 2010.
- 76. Andrus CH: Fluid and Electrolytes, Senior Student Capstone Lectures, Saint Louis University School of Medicine, March 24, 2010.
- 77. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, March 25, 2010.
- 78. Andrus CH: Junior Lectures, Department of Surgery, Saint Louis University School of Medicine, June 3, 2010.

- 79. Andrus CH: Course Director, ATLS Course #35375-P for Surgery Interns, Department of Surgery, Saint Louis University School of Medicine, June 26, 2010.
- 80. Andrus CH: "The Surgery Residency at Saint Louis University, (2010) Including the S.A.F.E.R. lecture for 2010-2011 Part of the 2010 Resident Orientation Symposia", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, June 30, 2010.
- 81. Andrus CH: "Resident Procedural Skills Simulation Center", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, July 7, 2010.
- 82. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, September 23, 2010.
- 83. Andrus CH, Hopping J, Hiler AM: "Common Bile Duct Stones in 2010" Case Presentation and Panel Discussion, Department of Surgery Grand Rounds, Saint Louis University School of Medicine, September 29, 2010.
- 84. Andrus CH: "Conducting an M&M Conference", Joint Grand Rounds of the Department of Surgery and Anesthesiology, Saint Louis University School of Medicine, October 6, 2010.
- 85. Andrus CH: Instructor, "Pediatric Trauma Module", Pediatric Advanced Life Support (PALS), SSM Cardinal Glennon Children's Hospital, October 12, 2010.
- 86. Andrus CH: Junior Lectures, Department of Surgery, Saint Louis University School of Medicine, December 2, 2010.
- 87. Andrus CH: Instructor, ATLS Course, Course #35256-P/SR, Saint Louis University Hospital, January 21, 2011.
- 88. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, February 10, 2011.
- 89. Hacker S, Andrus CH: "Trauma and the Pregnant Patient", Emergency Medicine Grand Rounds, Department of Surgery, Saint Louis University School of Medicine, February 15, 2011.
- 90. Andrus CH: Instructor, "Pediatric Trauma Module", Pediatric Advanced Life Support (PALS), SSM Cardinal Glennon Children's Hospital, March 15, 2011.
- 91. Andrus CH: "Report on the Recent Meeting of the Association of Program Directors in Surgery (APDS) and New Regulations for Residency Programs", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, April 26, 2011.
- 92. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, May 26, 2011.
- 93. Andrus CH: Surgery Resident Orientation, Department of Surgery, Saint Louis University School of Medicine, June 27, 2011.
- 94. Andrus CH: Course Director, ATLS Course #38216-P/SR for Surgery Interns, Department of Surgery, Saint Louis University School of Medicine, June 28-29, 2011.

- 95. Andrus CH: "The Functioning of the Surgery Residency at Saint Louis University, 2011", St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, June 29, 2011.
- 96. Andrus CH: "Resident Procedural Skills Simulation Center", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, July 6, 2011.
- 97. Andrus CH: "The History of Surgical Training", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, July 13, 2011.
- 98. Andrus CH: "The S.A.F.E.R. Lecture for 2011-2012", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, August 3, 2011.
- 99. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, August 4, 2011.
- 100. Andrus CH, Antal M: "ACGME General Competencies: Practice Based Learning and Systems Based Practice", St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, August 10, 2011.
- 101. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, August 11, 2011.
- 102. Andrus CH: "The Acute Infected Abdomen (Peritonitis)", St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, September 14, 2011.
- 103. Andrus CH: Instructor, ATLS Course, Course #39485-I, Saint Louis University Hospital, January 9, 2012.
- 104. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, January 26, 2012.
- 105. Andrus CH: "Update and Analysis of the Anonymous Resident Survery with Follow-up of the General Surgery Resident Committees of SLUSOM Of October 12, 2011", St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, February 1, 2012.
- 106. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, February 9, 2012.
- 107. Andrus CH: "Trauma in the Adult Women", Trauma Nurse Specialist (TNS) Course, Saint Louis University Hospital, February 10, 2012.
- 108. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, March 22, 2012.
- 109. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, May 10, 2012.
- 110. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, May 24, 2012.
- 111. Andrus CH: "The Functioning of the Surgery Residency at Saint Louis University, 2011", St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, June 27, 2012.

- 112. Andrus CH: Course Director, ATLS Course for Surgery Interns, Department of Surgery, Saint Louis University School of Medicine, June 28-29, 2012.
- 113. Andrus CH: "Resident Procedural Skills Simulation Center", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, July 11, 2012.
- 114. Andrus CH, Antal M: "ACGME General Competencies: Practice Based Learning and Systems Based Practice", St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, August 1, 2012.
- 115. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, August 2, 2012.
- 116. Andrus CH: "The S.A.F.E.R. Lecture for 2012-2013", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, August 8, 2012.
- 117. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, August 23, 2012.
- 118. Andrus CH: "The History of Surgical Training", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, August 29, 2012.
- 119. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, September 13, 2012.
- 120. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, October 11, 2012.
- 121. Andrus CH: Instructor, "Pediatric Trauma Resuscitation Module", Pediatric Advanced Life Support (PALS), SSM Cardinal Glennon Children's Hospital, October 23, 2012.
- 122. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, November 8, 2012.
- 123. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, November 29, 2012.
- 124. Andrus CH: "Kinematics of Trauma Lecture", Trauma Nurse Specialist (TNS) Course, Saint Louis University Hospital, January 25, 2013.
- 125. Andrus CH: "Blood Banking for the Surgeon", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, February 6, 2013.
- 126. Andrus CH: "Kinematics of Trauma" (Basic Science Lecture), Saint Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, February 13, 2013.
- 127. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, February 14, 2013.
- 128. Andrus CH: "Fluid and Electrolytes", Senior Student Capstone Lectures, Saint Louis University School of Medicine, March 20, 2013.
- 129. Andrus CH: "Blood Banking and Surgical Nutrition", Senior Student Capstone Lectures, Saint Louis University School of Medicine, March 21, 2013.

School of Medicine, April 4, 2013.

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- Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University
- 131. Andrus CH: Mock Orals of Senior Surgery Residents, Combined Departments of Surgery, Saint Louis University School of Medicine and Washington University School of Medicine, April 10, 2013.
- 132. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, May 16, 2013.
- 133. Andrus CH: "Resident Surgical Skills and Laparoscopic Lab for incoming Surgery Interns", Department of Surgery, Saint Louis University School of Medicine, June 24, 2013.
- 134. Andrus CH: "Resident Research Orientation for incoming Surgery Interns", Department of Surgery, Saint Louis University School of Medicine, June 24, 2013.
- 135. Andrus CH: "Fluid and Electrolytes, TPN, and Blood Component Therapy for incoming Surgery Interns", Department of Surgery, Saint Louis University School of Medicine, July 10, 2013.
- 136. Andrus CH, Antal M: "ACGME General Competencies: Practice Based Learning and Systems Based Practice", St. Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, July 31, 2013.
- 137. Andrus CH: Junior Student Lectures, Department of Surgery, Saint Louis University School of Medicine, August 1, 2013.
- 138. Andrus CH: "The S.A.F.E.R. Lecture for 2013-2014", Department of Surgery Grand Rounds, Saint Louis University School of Medicine, August 14, 2013.
- 139. McMellen M: "ABSITE review of Head and Neck", Andrus CH (mentor), Saint Louis University Surgery Grand Rounds, Saint Louis University School of Medicine, July 31, 2013.
- 140. Andrus CH: "Anterior Abdominal Wall, Inguinal Region, and Hernias", Freshman Medical Student Anatomy Course—Clinical Correlation, Saint Louis University School of Medicine, November 6, 2013.
- 141. Andrus CH: "Gastrointestinal System", Freshman Medical Student Anatomy Course—Clinical Correlation, Saint Louis University School of Medicine, November 7, 2013.
- 142. Andrus CH: Resident Skills Lab and also lecture on: Fluid, electrolytes, and how and why to write IV fluid orders, blood, and TPN. Lecture before new PGY-1 residents. SLUSOM, July 9, 2014
- 143. Andrus CH: Surgical Grand Rounds: ACGME General Competencies: Practice-based learning and Systems-based Practice (ACS NSQIP), SLUSOM, July 23, 2014.
- 144. Andrus CH: Surgical Grand Rounds: S.A.F.E.R. lecture, SLUSOM, Aug 13, 2014.
- 145. Andrus CH: Kinematics of Trauma. TNS Course (Trauma Nurse Specialist Course). SLUSOM, September 19, 2014.

- 146. Andrus CH: Appendicitis, Cholecystitis, and Biliary System, Junior Lecture, SLUSOM, January 15, 2015.
- 147. Andrus CH: Kinematics of Trauma. TNS Course (Trauma Nurse Specialist Course). SLUSOM, January 16, 2015.
- 148. Andrus CH: Lecture to junior medical students the first Monday of each 8-week rotation, Fluid and electrolyte lecture, SLUSOM, AY 2014-2015.
- 149. Andrus CH: Instructor of ATLS lectures and case scenarios, March 7, 2015.
- 150. Andrus CH: Capstone lecture to senior medical students, Fluid and electrolyte lecture, SLUSOM, March 12, 2015.
- 151. Andrus CH: Kinematics of Trauma. Department of Anesthesiology Grand Rounds, SLUSOM, May 13, 2015.
- 152. Participated as a General Surgery faculty member in the combined Washington University/SLUSOM Surgery Mock Orals, WUSOM, May 13, 2015.
- 153. Andrus CH: Faculty Judge of the ACS-MO Chapter Podium Sessions, Councilor, and Newly-elected Vice-President of the ACS-MO Chapter, Annual Meeting of the ACS-MO Chapter, Lake of the Ozarks, May 28-31, 2015.
- 154. Andrus CH: Research Opportunities at General Surgery Orientation in morning session and suture and instrument afternoon session, June 22, 2015.
- 155. Patel, Andrus CH: CVC lecture (Patel) and SIMS lab on CVC, chest tube placement, and foley placement for interns, July 8, 2015.
- 156. Andrus CH: Fluid, electrolytes, TPN, and blood component therapy lecture fore the interns, July 8, 2015.
- 157. Andrus CH: Surgical Grand Rounds: *Practice-based learning and systems-based practice*. July 15, 2015.
- 158. Andrus CH: Surgical Grand Rounds: S.A.F.E.R. lecturer. August 26, 2015.
- 159. Andrus CH: Anesthesiology Grand Rounds: A Surgeon's View of Blood Banking, December 2, 2015.
- 160. Andrus CH: Lecture to junior medical students the first Monday of each 8-week rotation, Fluid and electrolyte lecture, SLUSOM, AY 2015-2016.
- 161. Andrus CH: Capstone lecture to senior medical students, Fluid and electrolyte lecture, SLUSOM, March 12, 2016.
- 162. Participated as a General Surgery faculty member in the combined Washington University/SLUSOM Surgery Mock Orals, SLUSOM, May 5, 2016.
- 163. Andrus CH: PALS Trauma lecture and afternoon case scenario, June 23, 2016.
- 164. Andrus CH: Research Opportunities at General Surgery Orientation in morning session and suture and instrument afternoon session, June 27, 2016.

- 165. Patel, Andrus CH: CVC lecture (Patel) and SIMS lab on CVC, chest tube placement, and foley placement for interns, July 13, 2016.
- 166. Andrus CH: Surgical Grand Rounds: *Practice-based learning and systems-based practice*. August 24, 2016.
- 167. Andrus CH (moderator): Small group SCORE/True Learn Question Review: Inguinal and Femoral Hernias, Ventral Hernias, MIS Principles, September 14, 2016.
- 168. Andrus CH (moderator): Small group Mock Orals: Inguinal and Femoral Hernias, Ventral Hernias, MIS Principles, September 21, 2016.
- 169. Andrus CH (moderator): Small group SCORE/True Learn Question Review: Benign biliary 1 & 2, October 5, 2016.
- 170. Andrus CH (moderator): Small group Mock Orals: Benign biliary 1 & 2, October 12, 2016.
- 171. Andrus CH: Junior Medical Student lecture on Fluids, Electrolytes, Blood Components, and TPN: 8/29/2016, 10/25/2016.
- 172. Charles Andrus, M. D. and Catherine Wittgen, M.D., Co-chairpersons, weekly Surgery Grand Rounds and M&M conference
- 173. Andrus CH: Moderator, SCORE on first Wednesday of the month and Mock Orals for SLU residents the second Wednesday of the month: 9/14/2016, 9/21/2016; 10/5/2016, 10/12/2016; 11/9/2017, 11/16/2016; 12/14/2017; 2/1/2017, 2/8/2017; 3/1/2017, 3/8/2017; 4/5/2017, 4/12/2017.
- 174. Andrus CH: Surgery Intern Orientation: Procedures (Central lines, intubation, chest tubes) and the lecture on Fluids, Electrolytes, Blood component therapy, and TPN, Wednesday morning (~4 hours), 7/13/2016.
- 175. Andrus CH: The Core Competencies of Practice-Based Learning and Systems Based Practice, Grand Rounds, 8/24/2016.
- 176. Andrus CH: Senior Medical Student Capstone on Fluids, Electrolytes, Blood Component Therapy, 3/13/2017.
- 177. Washington U-SLU city-wide General Surgery Resident Mock Orals (8 hours at Washington University), 4/26/2017.
- 178. Andrus CH: The Core Competencies of Practice-Based Learning and Systems Based Practice, Grand Rounds, 7/19/2017.
- 179. Andrus CH: Surgery Intern Orientation: Procedures (Central lines, intubation, chest tubes) and the lecture on Fluids, Electrolytes, Blood component therapy, and TPN, Wednesday morning (~4 hours), 7/12/2017.
- 180. Andrus CH: Grand Rounds—Cholelithiasis + Epigastric Pain does not equal laparoscopic cholecystectomy—A surgeons study of H. pylori. Surgical Grand Rounds, Saint Loius University SOM, Department of Surgery, 1/31/2018.
- 181. Andrus CH: Kinematics of Trauma. TNS Course (Trauma Nurse Specialist Course). SLUSOM, February 23, 2018.

- 182. Andrus CH: Capstone lecture to senior medical students, Fluid and electrolyte lecture, TPN, and blood component therapy, SLUSOM, March 7, 2018.
- 183. Andrus CH: Wednesday small resident question review: "General Surgery topics in Thoracic Surgery", 4/11/2018.
- 184. Andrus CH: Wednesday small resident mock orals: "General Surgery topics in Thoracic Surgery", 4/18/2018.
- 185. Washington U-SLU city-wide General Surgery Resident Mock Orals (8 hours at St. Louis University), 5/9/2018.
- 186. Andrus CH: Extremes of Age lecture for ATLS, ATLS 2-day course for surgery residents, St. Louis University LRC, 6/28/2018.
- 187. Andrus CH: Faculty discussant for M&M conference. Surgery Intern Orientation: Procedures (Central lines, intubation, chest tubes) and the lecture on Fluids, Electrolytes, Blood component therapy, and TPN, Wednesday morning (~5 hours), 7/18/2018.
- 188. Andrus CH: Physician Vesting in One's Patients -- The Core Competencies of Practice-Based Learning and Systems Based Practice, Grand Rounds, 7/25/2018.
- 189. Andrus CH: Inguinal hernia repair in the 21st century. Department of Surgery Grand Rounds, Saint Louis University School of Medicine, 10/30/2019.

M. Supplemental Material:

I. Presentations (national and international meetings), seminars

- 1. Vernava AM, Andrus CH, Herrmann VM, Kaminski DL: Splenectomy for hematologic disease in adults. Presented as a poster at the Southwestern Surgical Congress in May, 1987, by A. Vernava.
- 2. Westfall SH, Andrus CH, Naunheim KS: A reproducible, safe jejunostomy replacement technique by a percutaneous endoscopic method. Presented at the annual SAGES meeting, April, 1989, by C. Andrus.
- 3. Rosato RM, Andrus CH: The effect of postoperative epidural analgesia on the duration of ileus in abdominal surgery. Presented at the Missouri Chapter of the American College of Surgeons, June, 1989, by R. Rosato.
- 4. Andrus CH, Dean PA, Ponsky JL: Evaluation of safe, effective intravenous sedation for utilization in endoscopic procedures. Presented as a poster at the World Congress of Surgical Endoscopy, March 15-17, 1990, Atlanta, GA, by C. Andrus.
- 5. German DS, Andrus CH: A simplified, reproducible, inexpensive method of compartmental pressure monitoring. Presented as a poster at the Southwestern Surgical Congress, April 22-25, 1990, LaQuinta, CA, by D. German.
- 6. Rosato RM, Andrus CH: The effect of postoperative epidural analgesia on the duration of ileus in abdominal surgery. Presented as a poster at the Southwestern Surgical Congress, April 22-25, 1990, LaQuinta, CA, by R. Rosato.
- 7. Andrus CH: Endoscopic ultrasonography: A new, highly sensitive and specific diagnostic and staging technique for upper gastrointestinal tumors. Oncology News Saint Louis University Medical Center, 4:1, 4, 1990.
- 8. Vernava AM, Beckman RF, Andrus CH, Johnson FE, Herrmann VM, Kaminski DL: Tangential colostomy preferred for temporary fecal diversion. Presented as a poster at the American Society of Colon and Rectal Surgeons, April 19 May 4, 1990, St. Louis, MO, by A. Vernava.
- Andrus CH, Daly JL: Utilization of an in-house generated quality assurance database for the evaluation of the surgical services in a large university-affiliated VA hospital.
 Presented at the Surgical Section of the Southern Medical Association, October 16, 1990, by C. Andrus.
- 10. Wittgen CM, Andrus CH, Fitzgerald SD, Baudendistel LJ, Dahms TE, Kaminski DL: Analysis of hemodynamic and ventilatory effects of laparoscopic cholecystectomy. Presented at the annual meeting of the Western Surgical Association, Scottsdale, AZ, November 14, 1990.
- 11. Andrus CH, Blatner ME, Wittgen CM, Kaminski DL: Cystic duct cholangiography during laparoscopic cholecystectomy. Presented at the Scientific Session of the Annual Business Meeting of the St. Louis Surgical Society, January 15, 1991.
- 12. Schneider TA, Andrus CH: The efficacy of endoscopic Congo red confirmation of completeness of proximal gastric vagotomy: An essential procedure. Pre-presented as a poster at the Annual Scientific Session of SAGES, Monterey, CA, April 17-19, 1991. (Won third prize out of 47 posters).

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- 13. Fitzgerald SD, Bailey PV, Liebscher GJ, Andrus CH: Laparoscopic cholecystectomy in anticoagulated patients. Presented as a poster at the Annual Scientific Session of SAGES, Monterey, CA, April 17-19, 1991.
- 14. Zegula HD, Esterl RM, Andrus CH, Wade TP: Anastomotic leak: A review of risk factors and methods of diagnosis and surgical treatment. Presented as a case report podium presentation at the Southwestern Surgical Congress, Las Vegas, NV, April 24, 1991.
- 15. Mehan DJ, Hagood P, Andrus CH, Parra R: Laparoscopic ligation of internal spermatic veins. A new surgical approach to the correction of varicoceles. (Video). Ninth World Congress on Endourology and ESWC, Vienna, Austria, June 20 & 22, 1991.
- 16. Naunheim KS, Petruska PJ, Roy T, Andrus CH, Johnson FE, Schlueter JM, Baue AE: Preoperative chemoradiation for esophageal carcinoma. Western Thoracic Surgical Association, Seattle, WA, June 28, 1991.
- 17. Wittgen CM, Andrus JP, Andrus CH, Kaminski DL: Cholecystectomy in the debilitated patient: Which procedure is best? 1991 Annual Professional Meeting of the Missouri Chapter of ACS, Lake of the Ozarks, MO, June 30, 1991.
- 18. Mehan DJ, Hagood P, Andrus C, Parra R: Laparoscopic ligation of internal spermatic vein. A new surgical approach to the correction of varicocele. 1991 Annual Professional Meeting of the Missouri Chapter of ACS, Lake of the Ozarks, MO, June 30, 1991.
- Schneider TA, Andrus CH: The efficacy of endoscopic Congo red confirmation of completeness of proximal gastric vagotomy: An essential procedure. 1991 Annual Professional Meeting of the Missouri Chapter of the ACS, Lake of the Ozarks, MO, June 29, 1991.
- 20. Andrus CH, Daly JL, Johnson FE, Wade TP, Kraybill WG, and Moley JF: Continuing evaluation and utilization of a VA Hospital in-house generated quality assurance surgical database. Presented to the Clinical Indicator Symposium, Department of Veteran's Affairs, August 26-29, 1991, Adam's Mark Hotel, St. Louis, MO.
- 21. Mehan DJ, Parra RO, Hagood PG, and Andrus C: Laparoscopic ligation of internal spermatic vein: A new surgical approach to the correction of varicocele. Presented at the 70th Annual Meeting of the South Central Section of the American Urological Association, November 17, 1991.
- 22. Parra RO, Andrus CH, Boullier JA: Staging laparoscopic pelvic lymph node dissection for adenocarcinoma of the prostate: Experience and indications. Presented at the Society of Surgical Oncology 1992 Annual Meeting, The Waldorf Astoria Hotel, New York, NY.
- 23. Schneider TA, Wittgen CM, Andrus CH, Kaminski DL: Comparison of minimally invasive methods of parietal cell vagotomy in a porcine model. Central Surgical Association, March 5, 1992.
- 24. Andrus CH, Wittgen CM, Naunheim KS, McManama GP, Rinehart GC, Clarkston WK, Wade TP: Densitometric evaluation of endoscopic ultrasonography. Poster presentation, ASGE, May 12, 1992.
- 25. Schneider TA, LaRegina MC, Fitzgerald SD, Wittgen CM, Virgo KS, Kaminski DL, Andrus CH: Confirmation of parietal cell distribution by histologic and Congo red techniques in a porcine model. Poster presentation, AGA, May 12, 1992.

- 26. Schneider TA, Wittgen CM, Andrus CH, Kaminski DL: Comparison of minimally invasive methods of parietal cell vagotomy in a porcine model. Missouri Chapter, American College of Surgeons, June 20, 1992.
- 27. Carr SC, Marts BC, Andrus CH, Kaminski DL, Wade TP: Staged surgical management of cholecystocutaneous abscesses. Presented as a poster to the Missouri Chapter, American College of Surgeons, June 20, 1992.
- 28. Wittgen CM, Andrus JP, Andrus CH, Kaminski DL: Cholecystectomy: Which procedure is best for the high risk patient? Presented as a podium presentation SAGES, Washington, DC, April 11, 1992, and the Third World Congress of Endoscopic Surgery, Bordeaux, France, June 18, 1992.
- 29. Mehan DJ, Andrus C, Parra O: Laparoscopic varicocelectomy [videorecording]/ report of a new technique to correct male infertility: Saint Louis University Medical Center. American College of Surgeons. Film Library. Woodbury, CT: Cine-Med,[1992], NLM 9414407, NLM Call Number WJ 780 VC no. 11 1992.
- 30. Neuberger TJ, Wittgen CM, Schneider TA, Andrus CH, Panneton WM, Kaminski DL: Evaluation of alternative PGV techniques in a chronic rat model. Poster presentation at Digestive Disease Week, ASGE Poster session, May 18, 1993.
- 31. Wittgen CM, Schneider TA, Fitzgerald SD, Panneton WM, La Regina MC, Johnson S, Kaminski DL, Andrus CH: Proximal gastric vagotomy by minimally invasive methods in an acute rat model. Podium presentation at the American College of Surgeons Missouri Chapter, June 20, 1993. (Dr. Wittgen won the 1st place resident's award for the presentation).
- 32. Schneider TA, La Regina MC, Fitzgerald SD, Wittgen CM, Virgo KS, Kaminski DL, Andrus CH: Confirmation of parietal cell vagotomy in a porcine model. Podium presentation, VA Surgeons, Augusta, Georgia, May 1, 1993.
- 33. Andrus CH: Laparoscopic cholecystectomy and physiologic changes. Department of Anesthesiology faculty, residents and nurses. Wednesday, November 30, 1994. Saint Louis University Medical Center, St. Louis, MO.
- 34. Esterl RM: Practical Pearls in Surgery: Gastrostomy tube obstruction. Contemporary Surgery 45 (6); Dec, 1994: 341.
- 35. Andrus CH: Endoscopy in the peptic ulcer patient. SAGES Flexible GI Endoscopy 1995, SAGES Annual Meeting, Orlando, Florida, March 11, 1995.
- 36. Andrus CH: Endoscopic approach to esophageal strictures. SAGES Flexible Endoscopy 1995, SAGES Annual Meeting, Orlando, Florida, March 11, 1995.
- 37. Andrus CH: "C.O.P.D.," Panel IV: Special problems in laparoscopy. SAGES Annual Meeting, Orlando, Florida, March 14, 1995.
- 38. Andrus CH: "New things in laparoscopy." Saint Louis University CME Outreach Program, March 25, 1995.
- 39. Andrus CH: The laparoscopic approach to the spine. Spinal Fracture Fixation, Practical Anatomy and Surgical Technique Workshop, St. Louis, MO, May 1-5, 1995.

- 40. Andrus C, et al: Evaluation of new methods of proximal gastric vagotomy (PGV). VA Research Improving Veteran's Care Poster Session. "VA National Research Week," St. Louis, MO, July 6, 1995.
- 41. Neuberger TJ, Andrus CH, Wittgen CM, Wade TP, Kaminski DL: Prospective comparison of helium versus carbon dioxide pneumoperitoneum. VA Research Improving Veteran's Care Poster Session, "VA National Research Week," St. Louis, MO, July 6, 1995.
- 42. Schneider TA, LaRegina ME, Fitzgerald SD, Wittgen CM, Virgo KS, Kaminski DL, Andrus CH: Confirmation of parietal cell distribution by histologic and congo red techniques in a porcine model. VA Research Improving Veteran's Care Poster Session, "VA National Research Week," St. Louis, MO, July 6, 1995.
- 43. Neuberger TJ, Wittgen CM, Schneider TA, Andrus CH, Panneton WM, Kaminski DL: Evaluation of alternative PGV techniques in a chronic rat model. VA Research Improving Veteran's Care Poster Session, "VA National Research Week," St. Louis, MO, July 6, 1995.
- 44. Andrus CH, Hinder R, Soper N: St. Louis Surgical Fundamental Forum: Laparoscopic Fundoplication (Specific Lecture: The St. Louis Experience to 1995), November 7, 1995.
- 45. Andrus CH: The Human GI System and Nutrition. Practical Anatomy and Surgical Technique Workshop, St. Louis, MO, January 24, 1996.
- 46. Andrus CH: Physiological Changes During Laparoscopy. M&M (Blue, Vascular, VAH, Colon/Rectal), Saint Louis University Medical Center, Department of Surgery, St. Louis, MO, February 28, 1996.
- 47. Andrus CH, Miller GA, Sunwoo YC, Nowlin LJ, Millis BM, JA Ellison, Qualls C: The quality assurance evaluation of an abdominal wound evisceration epidemic!? Poster Presentation for the 49th Annual Southwestern Surgical Congress, April 13-16, 1997, Rancho Mirage, CA.
- 48. El-Ghazzawy AG, Gupta N, Swope TJ, Kulkarni AD, Panneton WM, Robinson SM, Niehoff ML, Kaminski DL, Andrus CH: Evaluation of benzalkonium chloride chemoneurolytic proximal gastric vagotomy. Surg Endosc 11: 196, 1997. (Abstract & Poster Presentation for the Annual Scientific Meeting of the Society of American Gastrointestinal Endoscopic Surgeons, March 21-22, 1997, San Diego, CA.)
- 49. Andrus CH, Dries DJ, Romito PJ, Virgo KS: Rationing of surgical care is irrational in the VA. Presented before the Council of Surgery Service Chiefs, Annual Meeting of the Association of Veterans Affairs Surgeons, Louisville, KY, May 5, 1997.
- 50. Andrus CH: AVAS Council of Chiefs of Surgery representative to the NAVADP's "Physicians' Summit with Congress." Washington, D.C., November 4, 1997. Transcript of meeting published, U.S. Medicine 33 (23 & 24): 1, 29-46, 48, 51, 28; December, 1997.
- 51. Andrus CH: AVAS Council of Chief's Surgery representative to the NAVADP's "Physicians' Summit." Presented before the Council of Surgery Service Chiefs, Annual Meeting of the Association of Veterans Affairs Surgeons, Baltimore, Maryland, April, 1998.
- 52. Andrus CH: GI Bleeding. Multidisciplinary Critical Care Board Review Course. Society of Critical Care Medicine. Chicago, Illinois, August 13, 1998.

- 53. Andrus CH: GI Bleeding. Surgical Grand Rounds, Loyola University, Chicago, Maywood, IL, September 12, 1998.
- 54. Andrus CH: Minimally Invasive Surgery, Philippine Medical Association in Chicago, Westin Hotel O'Hare, Rosemont, IL, February 6, 1999.
- 55. Andrus CH, Johnson K, Pierce E, Romito PJ, Hartel P, Berrios-Guccione S, Best W: Finance modeling in the delivery of medical care in tertiary care hospitals in the Department of Veterans Affairs. Presented at the 23rd Annual Meeting Association of VA Surgeons, May 2, 1999. Accepted July 15, 1999 for publication, J Sur Res.
- 56. Andrus CH: Presentation of a summary of the "Edward Hines, Jr. Veterans Affairs Hospital Surgical and Anesthesia Services FY-99 Annual Report." to Congressional and Senatorial Staffers investigating the VISN 12 Delivery System Options Study (http://www.va.gov/cno/), November 23, 1999.
- 57. Andrus CH: Gastric Dyspepsia: From Beaumont to H. pylori. Loyola University Surgery Grand Rounds. November 11, 2000.
- 58. Andrus CH: Discussion with U.S. Congressman Henry Hyde, R-6th, and Congressional representatives of the Illinois Senators and northern Illinois Congressmen regarding the VISN 12 Options Study and CARES at the invitation of the Veterans for Unification. The Veterans for Unification Meeting, Broadview Public Library, Broadview, IL, August 30, 2000. This discussion resulted in two published articles:
 - 1. Wright C: VA hospitals studied again. (Westchester, IL: Westchester Herald, Pioneer Newspapers, Inc., Wednesday, September 6, 2000), vol 15, 24, pages 1, 3, 9.
 - 2. Wright C: VA hospitals studied again. (Hinsdale Edition: The Doings Newspapers, Pioneer Newspapers, Inc., Thursday, October 19, 2000), vol CVI, no. 3, page 35.
- 59. Andrus CH, Khuri SF, Daley J: Debate regarding the confidentiality and protection of quality assurance information of the VHA's NSQIP and CICSP. Annual Council of Chiefs meeting, Association of VA Surgeons, American College of Surgeons, October 22, 2000, Chicago, IL.
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- 96. Khouri AJ, Hou P, Andrus CH: Ischemic colitis in radiographic colonic lipohyperplasia: Getting it right for the wrong reason. MO-Chapter, American College of Surgeons, 52nd Annual Professional Meeting, Camden on the Lake, Lake of the Ozarks, Missouri, May 4, 2019.
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Brennan on Face the Nation of January 24, 2021: https://www.cbsnews.com/news/full-transcript-dr-deborah-birx-on-face-the-nation-january-24-2021.

Continuing Medical Educational (starting July 1, 2020 to present):

7/1/2020 – 6/30/2021: 21 Category 1 credits: Surgical Morbidity and Mortality Conference, VA St. Louis Health Care System – VIM04 FY21, Washington University in St. Louis School of Medicine, St. Louis, MO

7/1/2020 – 6/30/2021: 13 Category 1 credits: General Surgery Grand Rounds, Department of Surgery, Saint Louis University School of Medicine

7/1/2020 – 6/30/2021: 27 Category 1 credits: General Surgery Grand Rounds, Department of Surgery, Saint Louis University School of Medicine

Other Medical Educational Conferences. (starting July 1, 2020 to present)

7/27/2020	VA Core Values Training (I CARE Recommitment), VA TMS
7/27/2020	VHIE Overview Course, VA TMS
7/28/2020	Whistleblower Rights and Protections, VA TMS
7/28/2020	Ensuring Correct Surgery & Invasive Procedures and VHA Directive, VA TMS
8/17/2020	2015 HeartCode BLS, VA TMS
8/18/2020	Telehealth Emergency Plans Memorandum Self-Certification Course, VA TMS
8/18/2020	Telehealth to Home Using VA Video Connect Provider Training, VA TMS
8/19/2020	The EEO, D&I, No FEAR, and Whistleblower Rights and Protection Policy Statement, VA TMS
8/19/2020	Virtual Care Manager Training, VA TMS
8/19/2020	Managing Official Time in VA-TAS, VA TMS
9/14/2020	2015 HeartCode ACLS, VA TMS
9/21/2020	2015 HeartCode ACLS, VA TMS, VA TMS
12/24/2020	VA Caregiver Support Program Expansion Overview 101, VA TMS
4/26/2021	STL Basic Radiation Safety for Fluoroscopy, VA TMS
4/26/2021	STL Pain Management, VA TMS
4/26/2021	STL Preventing Surgical Site Infections: Best Practices, Better Outcomes, VA TMS
5/13/2021	VA Privacy and Information Security Awareness and Rules of Behavior, VA TMS
5/24/2021	Skills Training for Evaluation and Management of Suicide, VA TMS

Charles H. Andrus, M.D., F.A.C.S.

5/25/2021	Javelin Coaching Session with Steve Sons
6/1/2020	Javelin Coaching Session with Steve Sons
6/17/2020	Javelin Coaching Session with Fred Fishback –4939 125th Avenue, South, Wellington, FL 33449
6/24/2020	Javelin Coaching Session with Fred Fishback
8/9/2021	VA Core Values Training (I CARE Recommitment), VA TMS
7/8/2021	Javelin Coaching Session with Fred Fishback
8/9/2021	Prevention of Workplace Harassment/NoFEAR, VA TMS
8/9/2021	Privacy and HIPPA Training, VA TMS
8/9/2021	General Integrity and Compliance Awareness Training Test Out Option, VA TMS
8/10/2021	Government Ethics –The Essentials, VA TMS

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Revised 8/12/2019

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Married Pamela Bergkamp Andrus 7/27/87

Children Charles Harold Andrus - 1/25/87

Patrick Christopher Andrus - 3/18/89

Thomas Mark Andrus - 7/9/92 Michael Francis Andrus - 5/3/96 Timothy Stephen Andrus - 8/3/97

Birth Date March 28, 1953

Citizenship U.S.

Social Security Number XXX-XX-XXXX

Medicare 2018 XXX-XXX-XXXX

B. Education:

Undergraduate degree and major

University of San Francisco, 1971-1975 San Francisco, CA 94117 BS in Chemistry (Amer. Chemical Soc. approved degree) Summa cum Laude

Cal State University at San Francisco, 1973 (summers) 1600 Holloway Ave. San Francisco, CA 94132 General Zoology and General Botany

Graduate degree and major

Saint Louis University School of Medicine, 1975-79 1402 South Grand Blvd. St. Louis, MO 63104 M.D. conferred May 12, 1979

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The Dog Lab

Chapter

With many exotic new methods of conducting medical experiments including genetic testing and high technology in general, there remains a tried and true method of conducting the testing of innovative and potentially life-saving operations and procedures: the "dog lab." For the research physician, physiologist, and surgeon alike, the laboratory specializing in the use of large animals, e.g.: dogs, is the place that physicians are able to test procedures before they are attempted on human beings. Organ transplantation, the development of procedures using endoscopic instruments, the use of lasers to perform surgery on the human eye and even surgery through the use of remote controlled robots all had their beginnings in *The Dog Lab*.

Human nature is not only averse to being exposed to the grittiness of life but it collectively wretches in response to such exposures. As demonstrated by Hurricane Katrina in August of 2005, life's realities are stark, stomach turning and piercing. And yet, much of modern life is littered with a grittiness that we cannot indulge in the focus of the mind's eye. Whether it is the irresolvable nature and sordidness of abortion, the unimaginable, brutal and inhumane nature of the Nazi experiments on human beings or research of the Tuskegee Study of African Americans with syphilis in which penicillin was deliberately withheld in an effort to better understand how the disease is spread and what its effects are on the human body, we have little stomach for such mind numbing sordidness. The slaughtering of animals for their fur and for the protein flesh they provide for our daily fare comes even closer to scarring placid images of the good life as it is lived on a daily basis.

The use of dogs as vehicles for surgeons to learn how to perform new operations strikes a similar chord. It is abrasive to human consciousness to think that dogs are expendable for such purposes, especially since so many fellow citizens treasure them as family members. Dog labs are decades old and by nature experimental. Given their unsung role in the development of American surgical procedures, it is no small wonder that legions of dogs have

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been sacrificed on the altar of learning. As such, dog labs have come to represent a slaughter house of sorts, a place where the life of an animal is put at risk or sacrificed for the good of learning how to do something that would be of benefit to human kind. Due to the bloody and unsavory light in which the dog lab has come to be cast in the minds of surgical medicine, the dog lab has come to represent disparaging metaphor of sometime unconscionable practices.

Many years ago, the term "dog lab" was used as an instructional metaphor to then this newly named Veterans Administration (VA) hospital's Chief of Surgery. A fellow senior surgeon offered the term as a description and an explanation of how some physicians have historically viewed the relationship between VA hospitals in general and the medical schools with which they affiliated over the course of the last sixty years. Thus, historically, the metaphor epitomizes the derogatory sentiments and allusions that some physicians and medical educators have made in the presence of their educational charges regarding the indigent and less-fortunate who are treated in our nation's largest public hospital system.

The callous use of such a demeaning metaphor signals nothing less than a diminishment of human worth. In the verbal attitudes they express, all too often medical educators as role models convey implied values that impart heavy and unfortunately lasting meaning for their students. It is the method by which values both ill and good are transmitted over the course of generations. Even if untrue¹ initially and intended in reference to only one VA hospital, "The Dog Lab" is unimaginably derogatory to the U.S. Department of Veterans Affairs as an institution implying a substandard system of health care. Furthermore, it demeans and condemns those veterans who utilize the VA as their primary source of healthcare as somewhat less-than-human experimental subjects. And yet, it is the country's veterans who exposed themselves in harms' way to protect our way of life throughout our nation's history. It is those same veterans who knowingly served their country not knowing when they were inducted and swore allegiance to the country whether they would be stateside for the duration of their military career or die in combat within six months of their induction. It is those very same veterans to whom Abraham Lincoln 140 years ago promised on our behalf: "...to care for him who shall have borne the battle, and for his widow, and his orphan..." It is those veterans--the short, the long and the tall, the drug addicted or alcoholic, homeless, chronically mentally ill and rife with unrelenting PTSD--to whom we owe our way of life. The manner in which they are treated in the healthcare system dedicated to them reflects on the very character of our country.

¹VA hospitals have been recognized in recent studies as providing an above average standard of healthcare quality. See *U.S. News & World Report*. July 18, 2005

Chapter 3

Charles H. Andrus, M.D., F.A.C.S Former Chief, Surgical Service, Edward Hines, Jr. VAH Former Professor and Vice-chairman, Dept. of Surgery Loyola University, Chicago

Gerald Mozdzierz, Ph.D. Former Chief, Psychology Service, Edward Hines, Jr. VAH Former Chair, Edward Hines, Jr. VAH Ethics Committee Professor of Psychology, Loyola University, Chicago

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One definition of a scandal is: "A publicized incident that brings about disgrace or offends the moral sensibilities of society." While many will find in Dear Mr. President: "...to care for him who shall have borne the battle..." elements that are offensive at many levels, the incidents involved have never risen to the level of a Scandal. How society views moral insensibilities and chooses to acknowledge that such insensibilities exist are really the core issues within Dear Mr. President: "...to care for him who shall have borne the battle...". For an incident or series of incidents to become "scandalous" it is not merely that they are disgraceful or offend, but that they become known. Thus, Dear Mr. President: "...to care for him who shall have borne the battle..." was written solely to bring to public awareness that which exists that should offend the moral sensibilities of our society today.

The incidences that have been described in this book which should offend moral sensibilities are really isolated to individual patients even though collectively many have been at risk as was acknowledged indirectly in a recent publication.² (Over six years, 39,577 individuals underwent operation without the responsible attending surgeon-of-record present at the time of operation out of 610,660—6.48%) While 6.48% may be only one in fifteen patients, the practices of attending surgeon absenteeism were probably previously much higher and have been documented and known to the U.S. Department of Veterans Affairs and the affiliated universities for over thirty-five years.^{3,4} As such, attending surgeon absenteeism was not only condoned and possibly encouraged, but also institutionalized over the years.^{5,6}

Although most patients implicitly expect their "responsible attending" surgeon to be present in their individual operation, if the outcomes were equivalent, then one could possible argue that such practices were permissible as² "medical training is provided within a setting that allows an appropriate balance of supervision and independence without compromising outcomes, which makes VA hospitals a popular venue for physician trainees." If one carefully peruses the recent pivotal report² from key individuals (the majority being prominent attending surgeons) within the U.S. Department of Veterans Affairs, the touted acclamation "to allay any concerns about supervision of residents in the ORs within VA hospitals" is contradicted by the very data presented. In the report, absolute outcomes which are those not subject to author interpretation were all statistically significantly higher (with p values of <0.001) in the group where the attending surgeon was never physically present during any part of the operation, [i.e.: 30-day mortality rate (2.66% versus 2.34%); return to OR (10.24%) versus 8.19%); emergency cases (12.84% versus 6.79%)]. Unfortunately, not only have these outcomes been misrepresented by the aforementioned paper², but this bias has seemingly been validated by a "Position Paper" in the same November 2005 issue of The American Journal of Surgery 7: "A study just completed by Itani et al [7] shows that the former level 3 (attending supervision: attending immediately available, not in room) had not been associated with overall increased morbidity or mortality and, in fact, was protective." [Although the 30-day morbidity rate² (complication rate), which represents all documented complications other than death, was lower (8.27% versus 10.47%), the identification of a morbidity is observer/recorder dependent and not an absolute outcome parameter—that, is to say, the identification and reporting of complications--short of deaths--are like "beauty" perceived "in the eye of the beholder."]

In March 2006, I spoke by phone with Tim Flynn, M.D., F.A.C.S., Professor of Surgery and Dean for Graduate Medical Education at the University of Florida. In the years 2007-2008, Tim will be the Chairman of the American Board of Surgery. In a very real sense, Tim has been one of the few surgeons in this country that has been willing to listen or even speak with me. After I presented my paper on mortality outcomes and the presence of attending surgeons at the time of operation in Vancouver in 2003, it was he alone, at that time, who asked me to sit down with him and requested that I explain what had occurred that had stimulated me to pursue my focus on appropriate resident supervision.

Later, as conversations infrequently continued by phone, I raised the issue in March 2006 of the sentence in American Journal of Surgery position paper on patient care, surgical education, research, and faculty development: "A study just completed by Itani et al [7] shows that the former level 3 (attending supervision: attending immediately available, not in room) had not been associated with overall increased morbidity and mortality and, in fact, was protective." I heard kind of chuckle on the phone; and he did not correct me when I called such a statement incredibly stupid. He then advanced that the VA has changed. They are much more cognizant of resident supervision and the "compliance officers" are now monitoring attending physician presence at the VA (e.g. He gets a phone call from the compliance officer every time he has "core time" at the VA to confirm that he is physically present at the VA. (Core time is approximately 1/4th of the contractual weekly time agreed upon with the VA by the part-time attending physicians guaranteeing physical presence at specific times on the VA property.) He commented that recently the compliance officer confirmed on the phone's digital display that he was calling from an inside VA phone.) He then went on to state that indeed this type of surveillance had come about across the nation in the recent past.

I then made comment to the fact that we had fixed the problem without ever acknowledging that a problem existed. I stated that the mindset is still out there. I gave the example of the resident two years ago who in front of my fellow faculty members said that I, as an attending surgeon, had to let the junior residents make mistakes in the emergency room at night and on weekends so that they would not make the same mistakes when they went out into the real world. Tim concurred that such a statement was inappropriate. To my thought though, such a statement is condoned and permitted in our profession because we never admitted to any adverse outcomes publicly that resulted from inadequate attending surgeon supervision of residents in our public hospitals. In short, we have tacitly agreed to an ethic that is disparate in nature—the quality of the provision of medical care provided the individual patient is dependent on the social/economic class of the patient, the time of the day, and whether the attending surgeon feels like being present.

Tim concluded our conversation by stating that we must move ahead. It was his hope that during his next five years in academic medicine he will be able to advance the concept of graduated credentialing of surgery residents at the national level. With such a process, hopefully surgery residents will be appropriately supervised in their initial years by attending surgeons physically present in the operating room and also provided some independent operative experiences in their later years of training after operative competence demonstration and documentation (supervised by attending surgeons outside the operating room but immediately available in hospital). Although noble in the intention of advancing independent operative competence for the individual senior surgery resident within the structure of the formal residency, such a concept has the

inherent potential for abuse with regards to that which previously occurred in both the public and private sectors. Since the profession has never publicly acknowledged that about which is described in this text: *Dear Mr. President: "...to care for him who shall have borne the battle..."*, one can only anticipate that history will repeat itself in some form.

On March 4, 2004, the day after the hearing of the case Andrus v VA before the U.S. Court of Appeals for the Federal Circuit, accompanied by my wife, Pam, and my two oldest sons, we visited with the staffer of the U.S. House of Representatives Veterans Affairs committee with whom I had dealings for two years prior to that meeting. He brought us to an empty interview room in the House Office Building and began to explain to my wife, children, and myself his view of my involvement in what had transpired. He began by stating that having been in the military for many years, he had been instructed as to one form of bravery being defined by occurrences on the battlefield and that of a physical heroism. As he looked at my wife and children, he stated that Dr. Andrus has displayed the other form of bravery in which he had placed at risk his professional standing and financial solvency (and had lost) to stand by a principle. He stated that he doubted that I would ever be publicly acknowledged, but the system was slowly being pressured to change. By my providing information regarding resident supervision, I had helped provide the focus and direction for the Congress--and the VA was now being forced to change. It would not be a quick change--but it was now inevitable.

By that point in the conversation, my family was in tears. I was being told I had had my Pyrrhic victory and I should take consolation. Unfortunately, I may have succeeded in being part of the impetus for creating a new bureaucracy with compliance officers who would monitor attending surgeon presence at the VA. I had not affected the de facto mindset of the profession that "See one, do one"...under attending surgeon supervision was expected, but then "teach one"...without attending surgeon presence was still permissible in individual cases. James Cardinal Gibbons is quoted to have said a century ago: "Reform must come from within, not from without. You cannot legislate for virtue."

Although I may have slightly diminished the outward verbalization and expression of the Dog Lab mindset, it is doubtful many hearts were ever changed. Too often in our society today, we have been witnesses to individuals who have "gotten away with it." We have equated de facto that which is undiscoverable or legally minimized as not morally or ethically significant. It is easier to argue ethically in the abstract than to address that which is tangible—real patients who were provided their medical care disparately to their individual potential detriment. The Congressional staffer calling my actions and my positional stance brave may be right—but I don't feel like a hero. To have followed through in what I have attempted passionately to accomplish has, in my opinion, required tenacity of will to continue when others have chided me for my appeals and ignored and diminished my message; blind-resolve to purpose bordering on overzealous commitment; and, most of all, a tremendous amount of personal naiveté. In our present almost-narcissistic societal mindset, just so long as our actions don't directly affect us and are not anticipated to haunt us individually, there is little impetus today to champion "the just cause." When a physician is able to justify the necessity of adverse outcomes or minimize clinical errors suffered by the individual patient in the education of physicians-in-training, I think we should take pause for this is in contradistinction to that which has its origins 2,500 years ago: "do no harm." Obviously, no physician would

wish an adverse outcome to befall a loved-one for education sake. The pledge I expressed in 1990 at my initiation into the fellowship of the American College of Surgeons should be a universal axiom: "...Moreover, I promise to deal with each patient as I would wish to be dealt with were I in his position...."

By this point, the reader probably is questioning why the incidences and potential scandals that are related in *Dear Mr. President: "...to care for him who shall have borne the battle..."* have never risen to the consciousness of the American public. As the previous chapters have related, the issues have been known to many individuals and groups within the United States government, academia, the media, and religious organizations. Unfortunately, today—and probably throughout human existence—the risk of publicizing a controversy is always tempered by individual and institutional self-preservation agendas. Indeed, while individuals (e.g.: Anthony J. Principi, former Secretary of the U.S. Department of Veterans Affairs) and even institutions (e.g.: the AMA Committee on Ethical and Judicial Affairs) in private communications have been shocked, dismayed, or outraged and encouraging in my pursuit of correction of the problems in the supervision of surgery residents, no one has publicly acknowledged the problems. Why have none voiced these issues publicly?

One might look at the response to any significant social controversy displayed by individuals, organizations, and the government as a continuum much like a Gaussian distribution (a bell-shaped curve). The vast majority of individuals will be buffeted between those who are passionate in their response versus those that despair. With the progression of time, such a distribution is not static, though, for as the time-line of the controversy progresses, the involved entities may vacillate from both extremes--from the periods of elation to the depths of depression--but most will return to a central position of the majority.

In any human controversy, all that can be anticipated is possible resolution. Like the human response distribution to any controversy, the adjective describers of the resolution of such social conflicts are concomitantly variable and disparate: ethical, good, acceptable, unacceptable, criminal, unethical, immoral, morally-reprehensible, crimes against humanity, etc. In the resolution of any human ethical dilemma, one can only pray for a just and fair conclusion. After the Cuban missile crises of 1962 when our world had been on the brink of nuclear annihilation, President John Fitzgerald Kennedy stated before the graduates of the American University, June 10, 1963:

...What kind of peace do we seek?...Not the peace of the grave or the security of the slave. I am talking about genuine peace, the kind of peace that makes life on earth worth living, the kind that enables men and nations to grow and to hope and to build a better life for their children—not merely peace for Americans but peace for all men and women—not merely peace in our time but peace for all times....For, in the final analysis, our most basic common link is that we all inhabit this small planet. We all breathe the same air. We all cherish our children's future. And we are all mortal.

Medicine has been called one of the noblest of professions. Throughout the ages the Western World has professed the adherence to the principles of the Hippocratic Oath. As of late, the significance and adherence to many of the principals of the Oath have been diminished and dismissed. In the last century we have witnessed the complete antithesis

to adherence to the Oath personified in the Nazi medical experiments of World War II. Elie Wiesel, Professor of Religion and Philosophy at Boston University, Nobel Peace Prize recipient in 1986, and survivor of the Buchenwald concentration camp on April 2005 published Without Conscience in The New England Journal of Medicine:

...During the period of the past century that I call Night, medicine was practiced in certain places not to heal but to harm, not to fight off death but to serve it. In the conflict between Good and Evil during the Second World War, the infamous Nazi doctors played a crucial role. They preceded the torturers and assassins in the science of organized cruelty that we call the Holocaust. There is a Talmudic adage, quite disturbing, that applies to them: *Tov she-barofim le-gehinom*—"The best doctors are destined for hell." The Nazi doctors made hell.

Inspired by Nazi ideology and implemented by its apostles, eugenics and euthanasia in the late 1930s and early 1940s served no social necessity and had no scientific justification. Like a poison, they ultimately contaminated all intellectual activity in Germany. But the doctors were the precursors. How can we explain their betrayal? What made them forget or eclipse the **Hippocratic Oath**? What gagged their conscience? What happened to their humanity?

...In October 1939, several weeks after the beginning of hostilities, Hitler gave the first order concerning the *Gnadentod*, or "charitable death." On the 15th of that month, gas was used for the first time to kill "patients" in Poznán, Poland. But similar centers had already been created in Germany three years earlier. Now, psychiatrists other doctors collaborated in a professional atmosphere exemplary for its camaraderic and efficiency. In less than two years, 70,000 sick people disappeared into the gas chambers. The *Gnadentod* program was going so well that the head of the Wehrmacht Hospital psychiatric ward, Professor Wurth, worried, "With all the mentally ill being eliminated, who will want to pursue studies in the burgeoning field of psychiatry?" The program was interrupted only when the bishop of Münster, Clemens August Graf von Galen, had the courage to denounce it from his cathedral's pulpit; protest, in other words, came not from the medical profession, but from the church. Finally, public opinion moved: too many German families were directly affected.

Like the fanatical German theorists, Nazi doctors did their work without any crisis of conscience. They were convinced that by helping Hitler to realize his ambitions, they were contributing to the salvation of humanity. The eminent Nazi doctor responsible for "ethical" questions, Rudolf Ramm, did not hesitate to declare that "only an honest and moral person may become a good doctor."

The original movie, *The Exocist*, was probably one of the most horrifying movies ever produced by Hollywood. It portrayed nothing less than the **devil incarnate**. Unbeknown to most Americans, though, the storyline is based on historically recorded occurrences transcribed by Raymond Bishop, S.J. that transpired in St. Louis in the Spring of 1949. Many years later, through Thomas Allen's literary work, *Possessed*, the 26-page diary of Father Bishop related the story for public review of the reluctant exorcist, William Bowdern, S.J., the Pastor of St. Francis Xavier Church of St. Louis University. By the time I was a medical student and resident at St. Louis University, Father Bowdern was in retirement from St. Francis Xavier parish. As I now contemplate the collation and completion of *Dear Mr. President: "...to care for him who shall have borne the battle..."*, I marvel at how even minor transgressions and omissions on our part can affect adversely our fellow man.

Whether one is an atheist or believes in God or the devil, evil is always with us. President Abraham Lincoln was fictionally attributed in the 1960 Disney movie *Polyanna* to have stated: "When you look for the bad in mankind expecting to find, you surely will." Unfortunately, today we seldom look to see if our actions have wronged others for we have found that the denial of the evil we have incurred on others by our commissions or omissions can easily be discounted with arguments and other justifications. Our personal shortcomings and dereliction to our responsibilities can all too often be diminished, transferred to others, or wrongly alleged of the very institutions or individuals we have harmed. That is the evil incarnate that is pervasive in our society today. Truly, it is not just the fact that ghost and itinerant surgeries were practiced by many physicians and condoned by the universities and the VA that makes this story so tragic, but at every turn responsible individuals felt it justifiable to ignore what had become for some the *status quo*.

In stark contrast to that which I have related above and throughout this collection, I attended recently with our five boys and my wife the funeral of our children's former pediatrician, Austin "Roger" Sharp, M.D., who was a graduate of the University of Notre Dame and later St. Louis University School of Medicine. Although Dr. Sharp's son stated that his father never wished to be eulogized, his son stated that some honor was due his father whom he had observed was always there for his patients and who was also deeply committed to his family--reveling in all the facets of family life including outings and get-togethers even in the face of adversity (e.g., as when the old station wagon full of the family's children became disabled from vapor-lock during their vacation trek across the Kansas expanse). Lovingly, Dr. Sharp's son related that he remembered his father's dedication to the patients' families—on nights, on the weekends, and every other inconvenient time.

When in June 1990 our three-year-old son, Charlie (primary author of Chapter 4 of this book) had just survived acute pancreatitis and subsequent hemorrhagic shock induced by the anticonvulsant valproic acid and was still experiencing 200 myoclonic seizures per day, Dr. Sharp had asserted primacy in our son's care by calling a meeting of the specialists. As the pediatric specialists (neurologist and gastroenterologist) discussed the treatment options, Dr. Sharp took my wife and myself aside and stated: "I haven't a clue as to what is really going on with Charlie, but neither do they!" While it would be a decade later in a review article in *The New England Journal of Medicine* in which the constellation of mitochondrial encephalomyopathies would be described for the rank-and-file physician, Dr. Sharp's sincere personal assurance of his medical ignorance was more reassuring to my wife and myself than any platitudes, theories, or professional pontifications that had been or would be advanced regarding our son's condition. Indeed, the presence and concern of the attending physician that is visible to the individual patient represents the physician's personal validation to his patient and his personal allegiance to the intent of *primum non nocere* and the Hippocratic Oath.

Like Austin Sharp, M.D., Thomas A. Dooley, M.D., was also a graduate of the University of Notre Dame and St. Louis University School of Medicine. Dr. Dooley is known in history for specifically his establishment of rural clinics in Southeast Asia at the conclusion of the French Indochina War and more generally as a humanitarian of whom Albert Schweitzer, M.D. complimented with the paraphrase of Kahlil Gibran: "The significance of a man, Dr. Tom, is not in what he attains, but rather in what he longs to attain." Like Dr. Sharp, though, it was Thomas Dooley's concern for every patient that

makes his story so compelling. At the patient level, is not such commitment the outward expression of *primum non nocere*?

Even those who privately responded with acknowledgement of the aberrancies in attending surgeon supervision of surgery residents that transpired over the last half of century have never spoken publicly. Thus, the addenda to *Dear Mr. President: "...to care for him who shall have borne the battle..."* are, in part, really a collage of primary sources regarding the response to my pleas for review and self-reflection. Individually, the various correspondences may amount to little, while the collection may be a powerful commentary.

As a society and as institutions we have in the last decade hung our hats—so to speak—on quality assurance, continuous quality improvement, etc.¹ We have developed systems of review and methodologies to identify errors of miniscule proportions, and yet that which has been described in *Dear Mr. President: "...to care for him who shall have borne the battle...*" has essentially been ignored at every level in Academia, Medicine, and the U.S. Government. We, as a society today, have seemingly forgotten that which must be reiterated: "Reform must come from within, not from without. You cannot legislate for virtue."

President Harry S Truman has been reported to have had on his Oval Office desk a sign with the expression: "The buck stops here." In the final analysis, it was that admonition that drove my persistence in my attempts to raise the issues in *Dear Mr. President:* "...to care for him who shall have borne the battle..." before the Office of the Counsel to the President and the President of the United States of America. In his farewell address to the American people in January 1953, President Truman advised³:

The President—whoever he is—has to decide. He can't pass the buck to anybody. No one else can do the deciding for him. That's his job.

Let it be understood by every reader of *Dear Mr. President: "...to care for him who shall have borne the battle..."* that this anthology was <u>not</u> collated as a personal commentary on the degree of responsiveness of either the Clinton or Bush administrations to the issues raised. Rather, I have written this narrative to point out several significant moral axioms pertinent to our American society today and humanity throughout all times.

We should be ashamed when we ignore as individuals, as institutions, or as a society as a whole, our nation's promised adherence to protect and not deny the individual's rights⁴:

We hold these truths to be self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life. Liberty and the pursuit of Happiness.—That to secure these rights, Governments are instituted among Men, deriving their just powers from the consent of the governed.—that whenever any Form of Government becomes destructive of these ends, it is the Right of the People to alter or to abolish it, and to institute new Government, laying its foundation on such principles and organizing its powers in such form, as to them shall seem most likely to effect their Safety and Happiness. Prudence, indeed, will dictate that Governments long established should not be changed for light and transient causes; and

accordingly all experience hath sewn, that mankind are more disposed to suffer, while evils are sufferable, than to right themselves by abolishing the forms to which they are accustomed. But when a long train of abuses and usurpations, pursing invariably the same Object evinces a design to reduce them under absolute Despotism, it is their right, it is their duty, to throw off such Government, and to provide new Guards for their future security.

Demonstrable throughout our previous national imperfect history and aberrancies in our nation's universal protection of human rights (e.g.: slavery, the American-Japanese internment during World War II, Jim Crow laws, child labor exploitation, separate but equal, etc.), *Dear Mr. President: "...to care for him who shall have borne the battle..."* has attempted to outline the imperfectness and lack of adherence to that which we, as a people, profess.

It is anticipated that with the publication of Dear Mr. President: "...to care for him who shall have borne the battle...", the Veterans Health Administration of the U.S. Department of Veterans Affairs will attempt to diminish the significance of the narration. Attributable to the ongoing investigations and reports of the VA Office of the Inspector General⁵⁻⁷ over the last three years, individual attending surgeon and physician supervisory practices have been scrutinized and actively influenced by increased oversight by the Veterans Health Administration. While such increased scrutiny was indicated, some physicians have found such oversight burdensome or insulting as they now are being required to "punch a clock." Unfortunately, since neither the physicians nor the affiliated universities have ever publicly admitted to the issues outlined in Dear Mr. President: "...to care for him who shall have borne the battle...", it is unlikely that there will occur any fundamental change in physician mindset, attitudes towards the public hospital patients, or regard for the VA. Although that which is within *Dear Mr*. President: "...to care for him who shall have borne the battle..." is, at present, obscurely within the public domain⁸⁻¹¹ and being addressed and redressed as mentioned above, for most physicians the increased scrutiny and implemented documentation methodologies are annoying, bureaucratic, and non-sensible at best. By implementing correction without acknowledging the problems, we have failed to remember that: "Those who cannot remember the past are condemned to repeat it."12

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After one has perused the following narrative, I ask of the reader to take a moment for reflection. Ask what it will take to affect a change in the ingrained mindset regarding the disparate provision of medical care to individuals in our society based on economic or societal position. Can disparate attending physician attention to the individual patient be justified for the greater good of the educational experience? What will it take for society to address the issues raised in *Dear Mr. President: "...to care for him who shall have borne the battle..."*

This book asks of the physician a rededication to the principles and intent each individual physician has expressed in their swearing of the Hippocratic Oath. What will it take to affect such a change? How can these issues be brought to public awareness? Four hundred years ago, Shakespeare through Hamlet verbalized: "The play's the thing wherein I'll catch the conscious of the king." Hopefully, this book will be "the play" to catch the consciousness of physicians. There are still many role models out there like Austin Sharp, M.D., Thomas Dooley, M.D., and Albert Schweitzer, M.D. who place equal value and attentiveness on all their patients. As he was beatified in the process of determining sainthood on October 9, 2005 by Pope Benedict XVI, will it instead take a saintly individual like Cardinal Clemens August Graf von Galen mentioned in Without Conscience to affect a lasting change?

Unfortunately, the inherent evil to diminish the human worth of another individual by disparate treatment is all-too-easy and always present. Although many of our society's inequities were institutionalized during the founding of our country (e.g. slavery), it was the just philosophy that "all men are created equal" that should be the beacon for all—but especially the noble profession of medicine. To address the specific issues of physician absenteeism and the disparate provision of medical care to any member of our society, though, it is Francis W. Peabody, M.D.'s insightful admonition of seventy-five years ago that must become ingrained in the minds of all physicians to the end of time: "...for the secret in the care of the patient is in caring for the patient..."

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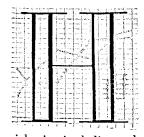
DECEMBER 1948

VOL. 179, NO. 6

Public Opinion Polls

Why did they fail? A leading authority assays their weaknesses and suggests some tested new techniques that would improve their accuracy

by Rensis Likert



OWEVER wrong George Gallup, Elmo Roper and other pollsters may have been in their forecasts of the recent election, no so-

cial scientist believes that public opinion polling itself was thereby discredited as a useful tool in social research. Actually it would be as foolish to abandon this field as it would be to give up any scientific inquiry which, because of faulty methods and analysis, produced inaccurate results. Science often learns more from mistakes than from successes. In this case, the polling fiasco of 1948 had at least two healthy results: 1) it demonstrated dramatically that polling as it is now conducted is far from being an exact science (which apparently needed public demonstration), and 2) it will force more rigorous standards upon the polling business.

It would take an exhaustive investigation to find out specifically where and how the election polls went wrong-if indeed that can ever be reliably determined. The poll results themselves were only partly responsible for the erroneous predictions; errors were also made in the analysis and interpretation of the results. Thus in the Gallup Poll, when the interviews were analyzed, a considerable block of voters was ignored. This was the group, constituting some eight per cent of all the voters interviewed, who said they were undecided and would give no indication of which presidential candidate they leaned toward. Gallup stated after the election that although four out of five of this group had voted Democratic in previous

in his predictions on the assumption that they would not go to the polls on election day. If his assumption was incorrect, this error might explain some of the discrepancy between Gallup's prediction of a 44.5 per cent vote for Truman and the 50 per cent the President actually received.

If the polls could be so inaccurate in predicting an election, what of their activities in sampling public opinion on complex social, economic and international issues? In that field there has been skepticism for some time. The skeptics have given many reasons for their doubts: the samples are too small or are otherwise inadequate; the problems are too complex to be dealt with in a few simple questions; the investigators are biased.

How valid are these criticisms? Just how sound are the present polling techniques, and how reliable are their results? The polls have had a great influence on political leaders, on the selection of candidates, and on the actions of legislators, government administrators and businessmen. This is an appropriate occasion for an analysis of the polls.

Polling Methods

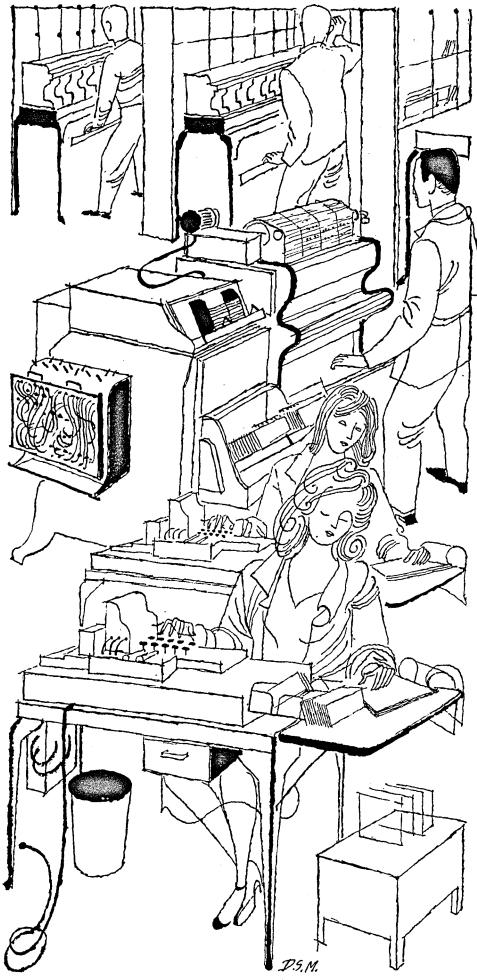
The polling process divides conveniently for study into two major parts: 1) the population sample used; 2) the questionnaire, the method of interviewing and the analysis of the replies. The accuracy of any poll obviously depends upon the accuracy of each of these parts.

Let us consider first the sample. Its importance was made plain by the dramatic failure of the Literary Digest Poll in 1936. That poll focused attention on the fact that the design of a sample is as important as its size. With a sample of more than two elections, these voters were disregarded million persons, the *Literary Digest* Poll variables that affect voting or other be-This submission is NOF for financial gain but for educational purposes only for ALL the American people

still had an error of 20 percentage points. This error had two sources. First, the poll was restricted to Literary Digest and telephone subscribers. Second, it obtained a biased sample of those subscribers, i.e., only those people who answer mailed questionnaires. The final sample therefore was not representative of the total population. So long as the voters who were not represented by the sample voted like those who were represented, the poll's predictions were borne out. But in 1936 this condition did not hold, and the poll accordingly went far astray.

The present public opinion polls use samples based on the so-called quotacontrolled method. This method depends for its accuracy on finding those variables that have a high correlation with the behavior being studied. Thus to design a sample for predicting an election, the pollsters determine how voting correlates with party affiliation, age, economic status, and so on. They then attempt to find out how these variables are distributed in the whole population, and finally they assign to each interviewer quotas based on this distribution of variables: the interviewer must poll a certain number of persons in each age group, socio-economic group, etc.

For maximum accuracy, however, a pollster would need to know all of the variables correlated with voting behavior, such as previous voting behavior, education, income, occupation, religion, party affiliation of the voter's father, mother and close friends, and so forth. He would also need precise information on the distribution of all these variables in the population. Unfortunately for public opinion polling, these two conditions almost never exist. In the first place, many of the



POLLING MACHINERY features the latest in business methods, such as punch tapes (foreground), tabulators (center) and mechanical sorters (rear), but saling and interviewing techniques used are not so up to date.

havior are unknown. In the second place, no data and labele on the distribution in the population of most of the variables that are known.

In spite of these difficulties, pollsters using the quota method have usually been able to make surprisingly accurate predictions. The methods generally employedare, briefly, as follows. Quotas are set, usually on the basis of geographical region, size of community, age, sex and socio-economic level. In some parts of the country, race also is included. In making election predictions, the results that these quota samples yield are generally tested by asking respondents how they voted in the previous presidential election and checking the percentages obtained with the actual election figures. Any discrepancy that exists is eliminated by weighting the results. For example, in a poll taken in Maine in 1944, 38 per cent of the persons interviewed said they planned to vote for Franklin D. Roosevelt. An analysis of the replies showed that the sample contained an under-representation of persons who had voted for Roosevelt in 1940. When a ratio correction was applied, a weighted estimate of 48 per cent for Roosevelt in 1944 was obtained.

This type of weighted correction has apparently sufficed to remedy the deficiencies in quota samples in most election polls in the past. There is always a possibility, however, that the high correlation between past and present voting behavior may change substantially for some important group not correctly represented in the sample, and in that case the error in the prediction may be large. It is conceivable, although there is no evidence on the point, that such a change may have occurred among some farm and labor groups in the 1948 elections.

Errors in the Samples

A major source of bias in quota samples is the fact that interviewers, in a perfectly human fashion, endeavor to fill their quotas in the easiest manner possible. They go to places where people are readily available and seek any who will fill the age, sex and socio-economic specifications of their quotas. They tend, therefore, to secure a sample which is biased in that it includes more people who are easily contacted than a truly representative sample should include. There is evidence also that some of the controls—for example, the socio-economic level—are vaguely defined.

An analysis of samples obtained with the quota-controlled method shows that this method tends to obtain data with biases which at times may be serious. For example, quota samples tend to include too few respondents from high income families. Thus analyses have shown that in typical quota samples in 1946 less than 10 per cent of the interviews were with for the families with an income of

\$5,000 or more. Census data for the same year show that actually about 15 per cent of the families had incomes of at least this amount. Quota samples also tend to have too few interviews with people of very low incomes. Another bias that often exists is the inclusion of too many persons who have at least completed high school and too few persons with grade-school education or less. Thus in typical quota samples about one third of the respondents have only a grade-school education or less, whereas census data indicate that the correct figure is about one-half.

The basic weakness of the quota-controlled method is that it does not employ a random sample. A general human failing among interviewers, or errors in the fixing of quotas, may produce a sample which is systematically biased in the same direction. In other words, when deliberate human choice enters into the final selection of respondents, the usual laws of probability governing the sampling phenomenon do not apply; the errors or deviations may not balance one another as they tend to do in a purely random sample, but at times may become cumulative and produce a bias of large and unpredictable dimensions.

A More Accurate Method

All this indicates that a method which rigorously follows random procedures will produce more accurate samples than the quota method can. Acting on this basis, a few Government and university groups have developed new methods of sampling which do indeed produce much more reliable results. These methods are called probability sampling. The fundamental requirement of probability sampling is that the final determination of just which persons are to be polled must be left to chance. Because this procedure is in conformity with statistical laws, it is possible to calculate precisely the probability that the margin of error in any sample will not exceed a given amount.

A method based on these principles is now being used by the U.S. Bureau of the Census, the Bureau of Agricultural Economics, Iowa State College Statistical Laboratory, the Survey Research Center of the University of Michigan, and other agencies. It is known as the area sample. The basic principle of this method is that each person in the population is given an equal, or known, chance to come into the sample. This is done by associating each person with one, and only one, very small geographic area and then selecting a random sample of the small geographic areas into which the country is thus divided.

The first step is to make a purely random selection of counties and metropolitan areas. Then within each of these areas a sub-sample of small geographic segments is selected, again by random methods. The final sample may include all the dwellings in each selected segment, or of sample desired. The selection of persons actually interviewed in each dwelling will then depend on the purpose of the survey; if its purpose is to predict an election, the sample will consist of all the eligible voters in the designated dwellings or certain voters selected at random.

When this method is used, the interviewer has no choice whatever. He goes to the specified dwelling and interviews the specified person or persons. If a respondent is not at home he calls again and again until he gets the interview; if he finds it impossible to do so, he reports that fact to headquarters.

Results

Area sampling eliminates the sources of bias present in quota-controlled samples. We do not need to know the variables affecting voters or their distribution in the population. We avoid human biases in selection of the persons to be interviewed. We can compute with confidence the limits or range of error for any result obtained-which is not possible in the case of quota samples.

The greater accuracy of the area sampling method has been amply proved in practice. The Survey Research Center at Michigan, using small nation-wide samples (500 to 3,500 persons) based on this method, has obtained results which check closely with census data and other reliable criteria. For example, a series of five sampling surveys was made between June, 1946, and October, 1948. The five samples were analyzed for certain characteristics—the percentage of white persons in the sample, the proportions in various age groups, the amount of schooling, and so on. To determine whether the samples were typical for the nation as a whole, the results obtained were then compared with U. S. Census figures. Comparing the survey of October, 1948, with the most nearly comparable census data, these were some of the results:

The data on racial distribution were close to the census figures. In the Survey Research Center sample, 91 per cent of the persons interviewed were white; the census figure for white persons in the whole population is 90.6 per cent.

With regard to age distribution, 23 per cent of the sample turned out to be in the group aged 21 to 29, and the census figure for the same group is 22.8 per cent; in the other age groups the correspondence was equally or almost equally close.

In the results on schooling, the proportion who had gone no farther than grade school was 44 per cent in this survey and 46.1 per cent in the census; those who had finished high school were 23 per cent of the sample, 22.9 per cent in the census; those who had finished college, 5 per cent of the sample, 5 per cent in the census.

These results were obtained with a random sample of only 1,151 persons The four other surveys in this series, using evengentallor of any bles (about 600 persons each), yielded approximately the same results; for example, the range in percentage of white persons in the four samples was from 89 to 91. Similarly consistent findings have been obtained in various area-sample surveys of family incomes and other variables in the popu-

Another kind of check has been made by expanding the results from a sample to an estimate for the nation as a whole. Thus in an area-sample survey made for the Federal Reserve Board in January and February, 1948, the Survey Research Center asked 3,562 households the amount of their 1947 money income; as a check, the average family income in this sample was multiplied by the number of private households in the nation, as estimated by the Census Bureau. The estimate of national income obtained in this way proved to be 10 per cent less than an estimate by the Department of Commerce based on aggregate data. As is to be expected, expansions of this kind show somewhat greater errors than direct comparison of percentages and frequency distributions.

The chief disadvantage of the area sample method is that it is more expensive. It costs more to design the sample and it costs much more for interviewers to take time to locate each designated respondent. But the increased accuracy of this method outweighs its additional cost. Because of the greater cost, most pollsters have resisted using probability samples and have adhered to the quota-sample method. Until the best available methods of sampling are used by those making election predictions and publishing polling results, it will be well to keep in mind that the sampling methods now employed can have a substantially larger error than is claimed. The formula now used by pollsters to compute the probable error in their polls is not applicable to quota samples; the formula is actually based on the assumption that the sample is truly random.

Interviewing

Now let us consider the other part of the polling process—the questions that are asked, the quality of the interviewing and the competence shown in the analysis and interpretation. Since these problems are somewhat different in a poll for predicting elections than in a poll measuring opinion and knowledge on social and economic issues, it will be well to discuss these two uses of polling separately.

In asking people how they plan to vote, there is little problem about the wording of the questions. People know the parties involved and know the major candidates. The names of the parties and the candidates have substantially the same meaning for all. There is a very real problem, however, in obtaining frank, unrestrained anevery kin dyrellings beling nother ignancial gain but for educational purposes unly for ALL the American people dures have been used to encourage respondents to answer accurately.

One of these is publicity, intended to inform people about the poll so they will be prepared to be interviewed. Gallup at times has had his interviewers wear badges. This publicity has incidentally produced a problem for the polls. People expect to be interviewed, and many become convinced, because neither they nor their friends are ever approached, that the poll results are fictitious and not based on actual interviews. Polls, however, use a sample of cities and counties, as well as a sample of people within these communities. Obviously, people who do not live in these particular sample points will never be interviewed. Moreover, only a very small proportion of the total U.S. population falls into any of the samples. No one should be surprised if he or his friends are never polled.

The pollsfers also try to win the cooperation of respondents by assuring them that their answers will be treated as confidential; the answers are not identified by name, but are used only to compile statistical totals. Sometimes the polls use a secret ballot. The interviewer carries a ballot box conspicuously locked with a padlock, and the respondent deposits his "ballot" in the box. The evidence varies on the usefulness of this method. In some tests it seems to have obtained more accurate answers, in others less satisfactory ones. Generally it appears to encourage voting by some of the persons who would otherwise answer "don't know."

One of the most useful devices is the indirect approach. Instead of asking the voter bluntly whether he is going to vote and, if so, for whom, the interviewer first asks a series of questions, such as how the voter feels about each of the major issues in the campaign, which of the candidates can best handle farm problems, high prices, the housing shortage, foreign policy, and so on. People who are reluctant to say whom they expect to vote for will almost always tell how they feel about the issues, how strongly they feel, and which candidate they believe will handle each of the different problems best. The answers to all these questions can then be analyzed to predict the probable proportion of each group who will vote and how they will

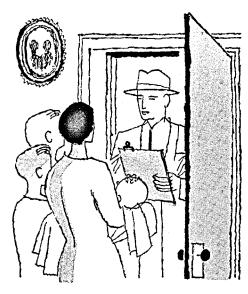
The prediction of elections involves a particularly knotty problem which often is neglected. This is the "turnout problem"-predicting who will vote. To predict an election it is not sufficient to know what candidates are favored; it is necessary to know what candidates are favored by those persons who will actually go to the polls. This means that the pollster must know which voters are most likely to vote and which most likely to stay home. Unfortunately, the pollsters have made

ure the intensity of the determination to vote, and the results consequently have a large possible error.

After the recent election, Gallup is reported to have stated that his polls indicated a relatively small turnout, but that he did not mention this large factor of uncertainty because his newspaper clients would have accused him of "hedging." As a rule, the larger the turnout, the greater the Democratic vote, but this rule may not have applied in this year's elections. In any case, it appears likely that the "undecided" vote and the size and character of the turnout played a large part in the miscalculations of the pollsters. Had they obtained more data on these factors and analyzed them adequately, their predictions might have been less positive and less wrong.

The Questions

The measurement of opinion on social, economic and international issues, and of



INTERVIEWER often biases sample by polling only people easy to reach.

public knowledge about these issues is more difficult, as a rule, than the prediction of elections. The problems in this field of polling are still so serious that opinionpoll results should be taken with even greater caution than predictions about elections.

Perhaps the greatest of these problems is that of meaning. Most of the issues of the day involve words and concepts that have different meanings for different people. On some issues large sections of the population may have no understanding of the major dimensions of the issue or the terms used. To understand the meaning of the percentages obtained in a poll, it is essential to know what respondents meant when they answered each question. Unfortunately, such data are not available. Yet polling results are often presented and that eaclPagepb24Centful26Gerstood the question and answered it from precisely the same point of view as that of the person conducting the poll.

An indication of the inadequacy of the usual polling questions can be obtained by asking a very small sample of respondents a question taken from any poll on a complex current problem and permitting these respondents to answer in their own words and to elaborate their answers. Several tests of polling questions have been made in this fashion. Quite consistently evidence has been obtained that questions on complex issues have different meanings for different people who are called upon to answer them.

Richard L. Crutchfield and Donald A. Gordon of Swarthmore College ran a test on the following Gallup Poll question which appeared in news releases of August 22, 1943:

"After the war, would you like to see many changes or reforms made in the United States, or would you rather have the country remain pretty much the way it was before the war?"

To test interpretations of this question, the investigators interviewed a cross-section sample of 114 New York City residents. After recording the respondent's initial reaction to the question, "the interviewer then encouraged the respondent to enlarge upon his answer in an informal conversational manner." The interviewers found that the initial response of their New York respondents gave substantially the same results as those obtained by Gallup for the country as a whole. But they also found that their respondents had seven different frames of reference in mind when answering the question. Some persons thought the question referred to "domestic changes or reforms"; others "technological changes"; others changes in the "basic political-economic structure of the U.S."; and still others thought it referred to changes in "foreign affairs of the U.S."

Respondents also had quite different meanings in mind when they answered "change" or "remain the same." For example, among those who answered in terms of "domestic changes and reforms" the word "change" for some persons meant shifts in a more liberal direction, such as "increases in social security," "higher pay levels," and "greater social equality for members of minority groups." Other persons meant a shift in the conservative direction, such as "change to a Republican administration," "less government control of business," and "more control of labor unions." Similarly, some of those who answered "remain the same" had in mind conservative aspects of our economy; others giving the same answer referred to liberal aspects, such as "maintaining high wages." It is obviously imposfew attempts to develop questions to meas—discussed with the implicit assumption, sible to interpret percentages which This submission is NOT for financial gain but for educational purposes only for ALL the American people combine into single totals answers which have such widely different meanings.

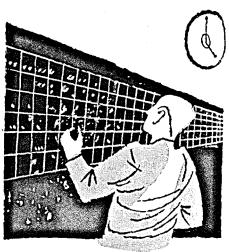
This study of what the respondents really meant by their answers substantially altered the interpretation of the poll, Thus in their first answers, 49 per cent of the New York City respondents said they wanted the country to "remain the same," and 46 per cent voted for "changes or reforms." But further questioning of those who were thinking in terms of domestic changes showed that 60 per cent wanted "changes or reforms," and 40 per cent favored "remain the same"-a direct reversal of the results with respect to this phase of the question. Most of those who thought the question meant technological change favored such change, while those who thought it referred to the basic political-economic structure of the U. S. did not want change.

Many of the polls dealing with complex current issues use questions which are very likely to be as misunderstood as was the question tested by Crutchfield and Gordon. The importance of knowing what questions mean to respondents and what the latter mean by their answers is illustrated by the following two questions, which seemed similar in wording but produced substantially different results. The Gallup Poll asked: "Do you think the U. S. and all the Western European countries participating in the Marshall Plan should join together in a permanent alliance—that is, agree to come to each other's defense immediately if any one of them is attacked?" The answers: Yes, 65 per cent; No, 21 per cent; No Opinion, 14 per cent. At about the same time (the results of both polls were published in the same week-May 31 and June 2, 1948), the National Opinion Research Center asked: "As you may know, England, France and other countries of Western Europe recently signed an agreement to defend each other against attack. Do you think the U.S. should promise to back up these countries with our armed forces if they are attacked by some other country?" The answers: Yes, 51 per cent; No, 39 per cent; No Opinion, 10 per cent. Thus on what was essentially the same question—the formation of a military alliance—there was a difference of 14 percentage points in the Yes answers and 18 points in the No answers. Unless data are obtained showing what respondents in a poll actually mean by their replies, the percentages obtained are of limited significance and sometimes may be seriously misleading.

The problem becomes even more difficult when attempts are made to take polls on complex issues in several different countries at the same time. The language and cultural differences, added to all the other difficulties, are likely to make the results seriously inaccurate. In an international poll it is virtually impossible to their use is likely to continue to increase, at the University of Michigan. This submission is NOT for financial gain but for educational purposes only for ALL the American people

have a complex question mean the same thing to all respondents.

There is no simple solution to this problem of the meaning of questions. One essential step is to analyze the problem in terms of psychological theories. This step works best when combined with a method of intensive interviewing using fixed questions and free answers. In using this technique, the polls would ask the respondent to select one of a number of alternative answers to a question, or would ask open questions, such as, "How do you feel about such and such a situation?" Interviewers would be trained to record the respondents' answers fully, and in the case of a question with alternative answers would encourage the respondent to elaborate his choice, using follow-up questions such as, "What do you have in mind?" The openquestion method and the fixed questionfree answer technique have demonstrated their usefulness in many tests. The major disadvantage of these methods, as with area sampling, is that they are somewhat'



STRATEGY BOARD in pollster's headquarters shows areas polled.

more expensive than the more conventional polling techniques. Here again, this disadvantage is outweighed by greater accuracy.

The Future of the Polls

Public opinion polling is a very young technique. None of the present polls was in existence 15 years ago. In less than 15 years the public opinion poll has become thoroughly established in this country, and it is gaining status rapidly in most of the rest of the world. The leaders of the polling business, particularly Gallup and Roper, are chiefly responsible for this achievement. The polls have been widely used by the public, by business and by government, and they affect many important decisions. Year by year their importance and use have increased. In spite of such failures as that in the recent election, Page 1244 of 1266 because polls employing sound methods can obtain essential information which is obtainable otherwise only at a prohibitive cost—as by a referendum—or not obtain-

The public opinion polls therefore have a tremendous responsibility. Their readers, including all those persons who make important policy and administrative decisions on the basis of their results, rely on the polls for accurate information. The polls must use methods which will assure that their results are reasonably accurate on all issues and at all times. In terms of their own self-interest, the polls must assume this responsibility. Indeed, their ability to regain public confidence may now depend on their willingness to restudy and improve their methods.

Among the methods now available which would permit them to measure opinion more accurately are probability sampling, the fixed question-free answer method of interviewing, open questions, questions employing an indirect approach, and the use of a series of interrelated questions covering the same phase of a particular issue from several different approaches. By using the best methods available, the polls will discharge more adequately their responsibility to the public, government officials and businessmen.

The public opinion poll is only one area of application of a far more important instrument: the sample interview survey. The sample interview survey is one of the research tools of the social sciences. It is being used increasingly to study such widely different problems as the behavior of consumers, the distribution of income, principles of organization and management, religious behavior, the factors affecting political behavior, the production plans of farmers, and the processes of propaganda. Either alone or in combination with experimental methods, this tool enables the social sciences to deal with their problems in a quantitative manner. Consequently, social scientists have taken a keen interest in this technique.

A great deal of research on improvements in the technique is now going on. Some of this research is being done by the public opinion polling agencies. More. however, is being done by the Federal government and educational and research organizations. Important methodological advances are flowing and will continue to flow from this research on all phases of polling, such as sampling, interviewing and research design. Social science is making available to the polls improved methods. It is to be hoped that the polls will accept and utilize them.

> Rensis Likert is the director of the Survey Research Center

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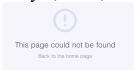
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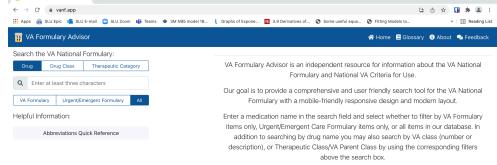
2020-11-01 Echevarria K: Remdesivir (VEKLURY) Criteria for use November 2020. U.S. Department of Veterans Affairs, Veteran Health Administration, VA Pharmacy Benefits Management Services 10P4P.

https://vanf.app/CFU_PDF/Remdesivir_VEKLURY_November2020.pdf

In my preparation of my dutiful submission in January 2022, when I attempted to access the URL above on January 5, 2022, the following came up:



When one clicks on: "Back to the home page" https://vanf.app/ one gets:



This is flagrant electronic destruction of official U.S. government documentation by a Service of an Agency of the Executive Branch of the U.S. Federal Government: VA Pharmacy Benefits Management Services 10PAP, Veterans Health Administration, U.S. Department of Veterans Affairs, which is overseen by Carolyn Clancy, M.D., M.A.C.P., VHA Deputy Under Secretary for Health (DUSH) for Discovery, Education & Affiliated Networks (DEAN). Below is the document that has been removed from the Internet that contains erroneous information in the "Inclusion Criteria."

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) CFU

Remdesivir (VEKLURY) Criteria for Use November 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS PAT COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See th	
300 011	ne VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.
Exc	clusion Criteria
If the	answer to ANY item below is met, then the patient should NOT receive remdesivir
	Treated for COVID-19 as an outpatient
	AST or ALT > 5 times the upper limit of normal
	Hospitalized patients but NOT requiring supplemental oxygen*
	Concomitant use of hydroxychloroquine or chloroquine
	Current eGFR < 30 mL/min**
Inc	lusion Criteria
The fo	ollowing must be fulfilled in order to meet criteria for remdesivir
	Hospitalized with SEVERE COVID-19 (room air oxygen saturation < 94%, requiring supplemental oxygen or increase from baseline if on chronic oxygen therapy or is requiring invasive or non-invasive ventilation or ECMO)***
Su	pplemental Information
or wh	mmended initial duration of therapy is 5 days, with the potential to extend to 10 days in patients who are not improving no remain critically ill. Therapy can be discontinued when the patient is appropriate for discharge, even if the full duration erapy has not been given
	n hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease may be appropriate and should be licated on a case by case basis
recom	ents with eGFR < 30 mL/min (or CrCl < 30-50 mL/min depending on the trial) were excluded from clinical trials and routine use is not immended by the manufacturer. Use may be considered and adjudicated on a case by case basis if the benefit is felt to outweigh the risks ecially when renal function is likely to improve rapidly (e.g. dehydration). The mechanism of calculating renal function can be based on I auidance.
local	emdesivir alone is not recommended alone for patients on mechanical ventilation or ECMO but may be considered in conjunction with

Updated version may be found at PBM INTERnet or PBM INTRAnet

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Investigational COVID-19 Convalescent Plasma -**Emergency INDs**

A licensed physician must request the Emergency IND (eIND) and obtain the COVID-19 convalescent plasma from a blood center. FDA does not provide COVID-19 convalescent plasma for eINDs.

 Investigational COVID-19 Convalescent Plasma - Emergency INDs Frequently Asked Questions (/media/136470/download)

March 24, 2020

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from public health threats including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to doing everything we can to provide timely response efforts to this pandemic and facilitate access to investigational drugs for use in patients with serious or immediately life-threatening COVID-19 infections.

One investigational treatment being explored for COVID-19 involves the use of convalescent plasma collected from recovered COVID-19 patients. It is possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. Although promising, convalescent plasma has not been shown to be effective in every disease studied. It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so. Investigators wishing to study the use of convalescent plasma are encouraged to submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR 312).

Although participation in clinical trials is one way for patients to obtain access to convalescent plasma, these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the expanding COVID-19 outbreak presents, while clinical trials are being conducted, FDA is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency Investigational New Drug Applications (eINDs) for Individual patients under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. This does not include the use of COVID-19 convalescent plasma for the prevention of infection.

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

Healthcare providers interested in the emergency use of investigational COVID-19 convalescent plasma under a single patient emergency IND should consider the following:

COVID 19 Convalescent Plasma

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Additional considerations for donor eligibility should be addressed, as follows:

- Prior diagnosis of COVID-19 documented by a laboratory test
- Complete resolution of symptoms at least 14 days prior to donation
- · Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at https://www.fda.gov/medical-devices/emergency-situationsmedical-devices/emergency-use-authorizations (/medical-devices/emergencysituations-medical-devices/emergency-use-authorizations).
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

Eligible patients for use under expanded access provisions:

- Must have laboratory confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19, for example:
 - Severe disease is defined as:
 - dyspnea,
 - respiratory frequency ≥ 30/min,
 - blood oxygen saturation ≤ 93%,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
 - lung infiltrates > 50% within 24 to 48 hours
 - Life-threatening disease is defined as:
 - respiratory failure,
 - septic shock, and/or

27/3/2020

Investigational COVID-19 Convalescent Plasma - Emergency INDs | FDA

- multiple organ dysfunction or failure
- Must provide informed consent

How to obtain authorization for use of COVID-19 convalescent plasma

- For request that are not highly time sensitive (response from FDA provided within 4 to 8 hours), the requesting physician may contact FDA by completing form 3926 (https://www.fda.gov/media/98616/download (/media/98616/download)) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov (mailto:CBER_eIND_Covid-19@FDA.HHS.gov).
 - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements of 21 CFR 312.305 and 312.310.
 - The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
 - · Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.
 - FDA will review the request and, upon approval, FDA will send the requesting physician a confirmatory email that includes the emergency IND number.
- In the event of an emergency that is highly time sensitive (response required in less than 4 hours) or where the provider is unable to complete and submit form 3926 due to extenuating circumstances, the provider may contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
 - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 15 working days of FDA's authorization of the use.

In addition to the above, FDA is continuing to work with its government partners including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to develop master protocols for use by multiple investigators in order to coordinate the collection and use of COVID-19 convalescent plasma.

¹Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention, JAMA, Published online February 24, 2020. doi:10.1001/jama.2020.2648

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-ober/investigational-covid-19-convale... 3/3

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RE: Phase 1 remdesivir trial result

Wed, Feb 16, 2022 3:26 pm

Andrus, Charles H. (STL) Charles.Andrus@va.govHide
TPublic Affairs Public_affairs@gilead.com

CAndrus, Charles H.

c(STL) Charles.Andrus@va.gov, candrus600@aol.com candrus600@aol.com, Anthony.Fauci @nih.hhs.gov Anthony.Fauci@nih.hhs.gov, kara.harris@nih.hhs.gov kara.harris@nih.hhs.gov ov, Janet.Woodcock@fda.hhs.gov Janet.Woodcock@fda.hhs.gov, Denise.Hinton@hhs.gov Denise.Hinton@hhs.gov, Jacqueline.OShaughnessy@fda.hhs.gov Jacqueline.OShaughnessy @fda.hhs.gov, Hogan, Michael R. (OGC) michael.hogan@va.gov

3 Andrus SLU cv 8_11_2021.docx (7.8 MB) 2/16/2022

NIAID Case #12276

Dear Gilead:

Thank you for forwarding this article to me: Humeniuk R. Mathias A, Huyen C, Osinusi A, Shen G, Chng E, Ling J, Wu A, German P: Safety, Tolerability, and Tolerability, and Pharmacokinetic of Remdesivir, An antiviral for Treatment of COVID-19, in Healthy Subjects. Clin Transl Sci 2020; 13, 896-906: Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID-19, in Healthy Subjects (wiley.com). I have attached a copy of my CV so you know who I am. Over my decades of involvement with the Veterans Health Administration (VHA), U.S. Department of Veterans, I have attempted to be an advocate for each and every individual Veteran patient that presented to me. My biggest challenge was to have the phrase in VHA Handbook 1400.1 on Resident Supervision revised (after ~50 years): Level 3: Attending Surgeon not present, immediately available. What was condoned by the inappropriate application of Level 3 was that on nights, weekends, holidays, family get togethers, etc., some University Attending Surgeons would staff residents in the OR from afar (ghost surgery). Twenty years ago, I fought for that change all the way to the U.S. Court of Appeals for the Federal Circuit in Andrus v VA, Case 03-3162—in which the court per curium "failed to rule." I lost all my battles with the VA; but, in the end, all Attending Surgeons-of-Record in the VA today are required to be present in the OR suite during every individual Veterans' operation which is definitely to the betterment of every Veteran patient. The VA saved face by: 1.) changing VAH Handbook from 1400.1 to VAH Handbook 1400.01 so you can't find previous versions electronically if you don't know the previous URL.; 2.) as is common practice today, in the agencies of the Executive Branch of the Federal Government, electronically overwrite documents without designating what has been rescinded or that there was even a previous document; and 3.) I became and still am an unperson in the VA from 4/1982-8/2016 since my Official Personnel File (OPF) has been misplaced/lost. Thus, from April 1982 to August 2016, I don't exist in the VA until I returned in August 2016, as an Attending Physician and General Surgeon at the St. Louis VAMC. My VA service from 1982 to 2002 does not exist "officially" even though from 8/1996 to 1/2002, I was the Chief of Surgery, Edward Hines, Jr. VAH (the first hospital of the University-VA affiliation in 1946 under PL-79-293); and I was interviewed for the position of Under Secretary for Health (USH) of the Veterans Health Administration (VHA), U.S. Department of Veterans Affairs (DVA) on the 10th floor of VACO (across Lafyette Square from The White House) on the afternoon of December 10, 1999. I am telling you this, so I can put in context for you the convoluted process regarding Remdesivir that parallels that which occurred to me in my fight to stop Physically Unsupervised resident surgeons by VA misdirection and obfuscation twenty years ago. Today, by changing URLs, electronic overwriting, and semantics, the FDA, the NIH, the CDC, the VA, etc. have somewhat stretched the truth before the American people.

I thank you for forwarding the reference regarding the Phase I studies completed for Remdesivir (RDV). As is quoted in the article:

On May 1, 2020, based on available data from to global clinical trials, the US Food and Drug Administration (FDA) granted emergency use authorization to allow RDV to treat adults and children hospitalized with severe COVID-19^{19,22,23} Based on these clinical data, RDV has been approved for the treatment of adults and pediatric patients in Japan.²⁴ This paper describes the safety and pharmacokinetics (PKs) of the solution and lyophilized formulations of i.v. RDV administered to healthy participants in the two first-in-human (FIH) phase I studies.

The above paragraph suggests that the FDA issued the EUA after review of the two first-in-human phase I studies involving Remdesivir (VEKLURY) and that review occurred at least by May 1, 2020, which means that phase I human trials were deemed safe and implies that the phase I trials *de facto* were completed—BUT, that presented multiple ethical and legal dilemmas for the FDA, the NIH, etc.

- 1. The FDA issued the first Remdesivir EUA on May 1, 2020 (which was the date when Dr. Fauci announced Remdesivir from the Oval Office); yet by making it an EUA, Remdesivir,-- the FDA was defining Remdesivir as an "unapproved" drug in the treatment of COVID-19.
- 2. As phase II/III clinical trials proceeded, prospective participants who had contracted COVID-19 should have been made aware in their Informed Consent that with The Right to Try Act, PL-115-176 that they could still be afforded Remdesivir by non-participation in the mandated RCT placebo trials—for that matter, all of America should have been told of this by the FDA! As the Phase I studies *de facto* were completed, any American could have asked for Remdesivir under PL-115-176 and should have received it!
- 3. As I am sure that you are well-aware that Remdesivir is "a single diastereomeric monophoramidate prodrug that inhibits viral RNA polymerases" which works best during the initial viremic phase of COVID-19—rather than in the later severe disease phases of cytokine cascade and bradykinin storm. Unfortunately, with the issuance of the EUA on May 1, 2020, "the US Food and Drug Administration (FDA) granted emergency use authorization to allow RDV to treat adults and children hospitalized with severe COVID-19¹⁹, 22, 23." In fact, the FDA removed the severity stipulation quietly--not notifying the American public of this significant retraction--on August 28, 2020. In the FDA January 21, 2022 letter to Madelyn Low, MBS, Manager, Regulatory Affairs, Gilead Sciences, Inc., https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fda-authorizationletter.pdf?la=en&hash=FD3737583BE0E4DF710ADB36AEAA2DBD, there are 8 references on pages 1 and 2 in which the Acting Chief Scientist of FDA outlined the chronology regarding Remdesivir including the August 28, 2020 retraction of the severity of illness stipulation: "...FDA revised authorized use of Veklury to no longer limit its use for the treatment of patients with severe disease." (How could Remdesivir being an "unapproved" drug in the treatment of COVID-19 under the FDA's EUAs standards become a drug that the FDA was officially revising authorization so it could be given early in the course of the disease? It seems like a bunch of semantics; but if that bunch of semantics limits the rights of individuals in America, that is wrong.
- 4. "On October 22, 2020, FDA also approved NDA 214787 for Veklury for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40

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- Kg) **requiring hospitalization."** At this point, Remdesivir (VEKLURY) was designated by the FDA as a prescription drug (NDA 214787) on October 22, 2020.
- 5. In November 2020, the Veterans Health Administration (VHA) of the U.S. Department of Veterans Affairs issued for the fully-FDA-authorized-prescription drug, VEKLURY, NDA 214787 the: "Remdesivir (VEKLURY) Criteria for Use" of how to administer Remdesivir with the severity Inclusion Criteria exclusively included that had been removed previously on August 28, 2020 by the FDA:

- 6. When I had a patient denied Remdesivir by the Infectious Diseases service quoting the November VA directive, I contacted Richard Stone, M.D., VHA Chief Medical Executive (the Trump Administration's title for the Under Secretary for Health, VHA, DVA). Dr. Stone contacted VA Pharmacy Management Services and the Medical Advisory Board. At first, the VA responded to me. But when the VA became evasive, I contacted the FDA, the NIAID (Case #12276), and wrote a letter to the editors of the *The New England Journal of Medicine*. None responded to me.
- 7. I recently had a patient admitted to the Surgical Service who had newly turned COVID-19 positive (less than 24 hours from negative to positive). The recommendations from the same Infectious Diseases service was that if the patient had any symptomatology like headache or neck pain, give three days of Remdesivir; and if the patient develops a cough, give five days of Remdesivir and dexamethasone. By the time of that consult, the CDC had stated a month before that Regeneron's and Eli Lilly's monoclonal cocktails were ineffective against COVID-19, omicron variant; and, thus, GlaxoSmithKline's sotrovimab was and is being de facto rationed at present time.

Once again, I thank all involved in addressing my question at Gilead regarding if a phase I study had been completed in the case of Remdesivir. You were all very professional and willing to listen—and, most of all, my personal thanks as a Federal Physician and Surgeon for you have provided this information which may become an outstanding service for the people of the United States of America.

Thank you,

Charles Andrus, M.D., F.A.C.S.

Professor, Department of Surgery, Saint Louis University School of Medicine

Chief and Attending General Surgeon, Unit II (SLU) General Surgery division, Surgical Service, John

Cochran (112JC), St. Louis, MO 63106 Office phone: 314-652-4100 ext 54463

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P.S. I hope this e-mail will initiate an overall discussion regarding transparency by the agencies of the U.S. Government in regards to the EARLY (< 72 hours from diagnosis) administration with intent of synergism of COVID-19 Convalescent Plasma, COVID-19 monoclonal antibodies, Remdesivir and other future antivirals, etc. Respectfully, Charles H. Andrus, M.D., F.A.C.S.

From: Public Affairs < Public affairs@gilead.com>
Sent: Wednesday, February 16, 2022 7:54 AM

To: Andrus, Charles H. (STL) < Charles.Andrus@va.gov> **Subject:** [EXTERNAL] Phase 1 remdesivir trial results

Dr. Andrus,

You can find the published results of the Phase 1 remdesivir trial here: https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.12840.

Thank you for your inquiry,

Gilead Public Affairs

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Reply Reply All Forward

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